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Higher mortality risk from gynaecological neoplasms and non-Hodgkin's lymphoma in patients with systemic lupus erythematosus: an observational study from the Spanish National Registry

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ABSTRACT

Objective To evaluate the impact of the different types of neoplasms and lineages on mortality of patients with SLE.

Methods Retrospective and observational comparison of the neoplasm-related deaths in patients with SLE and the general Spanish population reported in the Spanish Hospital Discharge Database. To determine the impact of SLE on the risk of dying from each neoplasm lineage, a binary logistic regression considering age, female sex, tobacco and alcohol consumption, was performed.

Results During 2016–2019, 139 531 in-hospital deaths from neoplasms were certified in Spain (91 in patients with SLE). Patients with SLE presented a lower mortality rate from solid organ neoplasms, (80.2% vs 91.1%, OR 0.393), linked to their lower risk of colorectal carcinoma (1.1% vs 10.8%, OR 0.110). By contrast, gynaecological neoplasms presented a higher risk (8.8% vs 3%, OR 3.039) in the deceased patients with SLE, associated with the higher frequency of vulvar neoplasms (2% vs 0.2%, OR 14.767) and cervical carcinomas (3.3% vs 0.5%, OR 3.809). Haematological neoplasm-related deaths were also more prevalent in patients with SLE (19.8% vs 8.9%, OR 2.546), mostly attributable to the higher proportion of deaths due to non-Hodgkin's lymphoma (11% vs 2.9%, OR 4.060) of B cell lineage (9.9% vs 2.5%, OR 4.133).

Conclusions Patients with SLE present a higher risk of death from vulvar neoplasms, cervical carcinomas and B-cell non-Hodgkin's lymphoma in comparison with the general Spanish population. In addition to developing strategies that might help to attenuate their occurrence and impact, such as decreasing the immunosuppressive burden, specific early detection programmes for these conditions should be investigated and considered carefully.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Mortality is twofold to fivefold higher in patients with SLE than in the general population.

⇒ Cardiovascular disease, infections and neoplasms, other than disease itself, impact on mortality of patients with SLE.

WHAT THIS STUDY ADDS

⇒ Patients with SLE present a higher risk of death from vulvar neoplasms, cervical carcinomas and lymphoma than matched population.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Decreasing the immunosuppressive burden and factors related to carcinogenesis should be priorities in these patients.

⇒ Specific early detection programmes for these conditions should be investigated and considered carefully.

INTRODUCTION

SLE is a chronic, inflammatory, autoimmune disease with multisystem involvement.[1 2] However, it is an extraordinarily complex condition with a wide variety of clinical features and phenotypes. SLE mainly affects young women who suffer from chronic inflammation, flares and cumulative drug toxicity.[3 4] Thus, this population presents a high burden from the disease from a young age. Mortality is twofold to fivefold higher in patients with SLE than in the age-matched and sex-matched population, confirming that there is still a lot of room for improvement.[5 6]

However, thanks to recent advances and better management of the disease, the prognosis of patients with SLE has dramatically improved in recent decades.[5 7] In parallel with the development of more efficient and less harmful treatments, the long-term

complications of SLE have become more important, such as the high prevalence of cardiovascular disease, the risk of neoplasms and the impact on quality of life, among others.[8–10] Here, several reports have evaluated the incidence of certain neoplasms in patients with SLE, since both the disease itself and subsequent chronic inflammation or immune system dysregulation, as well as the drugs prescribed and immunosuppression, can lead to a higher cancer risk.[11–13] However, some of these studies were limited by sample size and monocentric design, often with an insufficient follow-up period.[13–16] In addition, most of the previous studies analysed the incidence or absolute cancer risk, and not specifically mortality from certain neoplasm types and lineages, which in turn requires a higher population size and comparison with the general population.

In light of the above, our objective was to evaluate the impact of the different types of neoplasms and lineages on mortality of patients with SLE in a nationwide analysis conducted in Spain, a country with a population of 47 million.

MATERIALS AND METHODS

A retrospective study with data from population-based hospital discharge diagnosis at the Minimum Basic Data Set of the Spanish Registry of Hospital Discharges was performed. This is a national public access registry belonging to the Spanish Ministry of Health. The Spanish National Hospital Discharge Database (SNHDD) includes demographic and epidemiological data and up to 20 discharge diagnoses carried out during admission and defined from 1 January 2016 by the International Classification of Diseases, Tenth Revision (ICD-10). In this database, the main diagnosis is considered the defining reason for admission, and the cause of death if that occurred. Prior studies have been performed on this registry for other illnesses, including infectious or autoimmune diseases, confirming its high value for producing estimates of current burden and epidemiology of clinical conditions and causes of death.[17–19]

In the present study, we compared the epidemiological and demographic data, as well as the proportion of deaths attributable to the distinct neoplasm types and lineages, of the patients with SLE with the general Spanish population.

The data were provided after all potential patient identifiers had been deleted and data were given anonymously.

Study population

We selected hospital admissions, from 2016 to 2019, for patients with a diagnosis within the ICD-10, Clinical Modification (ICD-10-CM) code M32 (SLE) at any position in the diagnostic list. Patients who presented drug-related SLE (ICD-10 code M32.0), or secondary Sjögren's syndrome (ICD-10 code M35.0), were excluded since both conditions might impact the neoplasm-related risk in the population with SLE.[20]

In parallel, all the in-hospital deaths attributable to neoplasms (from ICD-10-CM code C.00 to D.49) in the same period were retrieved from the SNHDD, and were used as the control group to compare with the patients with SLE. Neoplasm-related deaths were classified as follows: malign neoplasms, including solid organ malign neoplasms (C00-C80), haematological malign neoplasms (C81-C96), in situ neoplasms (D00-D09), benign solid organ neoplasms (SON) (D10–D36 and D3A) and unknown or non-specified behaviour neoplasms (D37–D49), in turn also including SON and haematological neoplasms (HN). Myelodysplastic syndromes (MDS), based on their worse prognosis and mortality rate, were considered malign HN. Finally, the main SON and HN lineages, and subsequent subclassifications, such as gastrointestinal, lung, breast, gynaecological, urological, together with lymphoma, leukaemia or MDS, among others, were considered and analysed separately.

Statistical analysis

Categorical variables were reported as frequencies and percentages while continuous variables were presented as mean and SD. The significance of differences between the two groups was determined by the χ^2 test or Student's t-test, as appropriate. To determine the impact of SLE on the risk of dying from each neoplasm group and lineage, we performed a binary logistic regression analysis, considering age of female sex, tobacco and alcohol consumption (according to ICD-10 CM codes F17 or Z72.0 and F10, K70 or I42.6, respectively) for each neoplasm group and lineage. For all the analyses, a significance level of 0.05 was set. Statistical analysis was performed using SPSS V.26.0 (IBM, Spain).

RESULTS

Characteristics of patients with SLE

Between 2016 and 2019, 25 344 hospital admissions of patients with SLE were identified in the Spanish National Registry. The admissions of patients with drug-induced SLE (123, 0.5%), as well as those with secondary Sjögren's syndrome (1.879, 7.4%) were excluded as discussed above. Table 1 shows the population characteristics of the remaining 23 341 admissions. Overall, 82.2% were female, with a mean age of 53.2 years. Prior or current lupus nephritis was identified in 5694 (22.6%) of the patients and antiphospholipid syndrome in 2304 (9.9%). 1429 (6.1%) patients were admitted to the intensive care unit and 739 (3.2%) died. Of the deceased, 36 patients (4.9%) died as a result of SLE activity and 91 (12.3%) from neoplasms (p<0.001). The mean length of admission was 8.5 days.

Differences in neoplasm-related deaths in patients with SLE and the general Spanish population

The mean Spanish population between 2016 and 2019 was 46 704 229 inhabitants. In this period, 705 557 in-hospital deaths were identified, 139 531 (19.8%) being from neoplasms (online supplemental table 1). Overall, 127

Table 1 Patient characteristics

Admission of patients with SLE (n=23 341)	
Patient/Admission characteristics	
Female, n (%)	19 191 (82.2)
Age (years) (mean, SD)	53.2 (18.6)
SLE activity-related admission, n (%)	4385 (18.8)
Lupus nephritis, n (%)	5694 (22.6)
Antiphospholipid syndrome, n (%)	2304 (9.9)
Outcomes	
Deaths, n (%)	739 (3.2)
Admission length (days) (mean, SD)	8.5 (16.4)
ICU admission, n (%)	1429 (6.1)
ICU admission length (days) (mean, SD)	6 (10.8)

ICU, intensive care unit.

153 (91.1%) of these deaths were related to SON and 12 378 (8.9%) to HN.

Table 2 identifies several differences when the proportion of neoplasm-related deaths in patients with SLE was compared with the general Spanish population. Ninety-one patients with SLE died from neoplasm (12.3% vs 19.8%, p=0.002). Deceased patients with SLE from neoplasm were younger than the general Spanish population (64.8 vs 70.7 years, p<0.001).

In patients with SLE, 80.2% of neoplasm-related deaths were attributable to SON (vs 91.1% in the general Spanish population, p=0.001) and 19.8% to HN (vs 8.9% in the Spanish population, p=0.001). In addition, the mean age of patients with SLE who died from neoplasms (64.8 vs 70.7, p<0.001) and from SON (63.9 vs 70.6 years, p<0.001) was lower than that of the general population. No age differences were found in the HN-related deaths between the two groups (68.3 vs 71.9 years, p=0.333).

Since the rate of SON and HN deaths differed in patients with SLE and the general Spanish population, a more detailed comparison, considering the different neoplasm lineages, was performed (tables 3 and 4). In order to determine the impact of SLE on the risk of death from certain neoplasms, a binary logistic regression analysis, taking into account age, sex, alcohol and tobacco consumption, was carried out for each neoplasm lineage (figures 1 and 2).

Solid organ neoplasms

Considering deaths from neoplasms in the total Spanish population, patients with SLE presented a lower mortality frequency and risk of digestive neoplasms (14.3% vs 29.8% p<0.001, OR 0.423, 95% CI 0.240 to 0.747), including gastrointestinal tract neoplasms (5.5% vs 17.6%, p<0.001, OR 0.318, 95% CI 0.129 to 0.784) and colorectal carcinoma (1.1% vs 10.8%, p<0.001, OR 0.110, 95% CI 0.015 to 0.789) (table 3, figure 1). Similarly, the mean age of the patients who died from digestive (61.5 vs 73 years, p<0.001), gastrointestinal tract neoplasms (57.4 vs 73.7, p=0.004) and colorectal carcinoma (48 vs 75.1 years, p=0.027) was significantly lower in patients with SLE.

However, considering the total amount of death from neoplasms, patients with SLE presented a significantly higher gynaecological neoplasm death rate (8.8% vs 3%, p=0.006) and risk (OR 3.039, 95% CI 1.465 to 6.307), resulting from the higher frequency of vulvar neoplasms (2% vs 0.2%, p=0.0017, OR 14.767, 95% CI 3.587 to 60.792) and cervical carcinomas (3.3% vs 0.5%, p=0.011, OR 3.809, 95% CI 1.182 to 12.272) (table 3, figure 1). No age differences between the two populations were found for gynaecological neoplasms.

Table 2 Differences in neoplasm-related deaths for patients with SLE and the general Spanish population for the period 2016–2019

	Neoplasm-related deaths n (%)			Mean age (years) (SD)		
	Non-SLE	SLE	P value	Non-SLE	SLE	P value
Total	139 440	91	–	70.7 (13.5)	64.8 (12.4)	**<0.001**
SON	127 080 (91.1)	73 (80.2)	**0.001**	70.6 (13.3)	63.9 (12.5)	**<0.001**
HN	12 360 (8.9)	18 (19.8)	**0.001**	71.9 (15.5)	68.3 (11.7)	0.333
Malign neoplasm	136 792 (98.1)	90 (98.9)	1	70.6 (13.5)	64.9 (12.5)	**0.001**
Malign SON	124 831 (89.5)	72 (79.1)	**0.003**	70.5 (13.3)	64 (12.6)	**<0.001**
Malign HN	11 989 (8.6)	18 (19.8)	**0.001**	71.7 (15.6)	68.3 (11.7)	0.366
Benign SON	727 (0.5)	0	0.596	72.3 (13.5)	–	–
UB neoplasm	1698 (1.2)	0	0.632	78.7 (13.8)	–	–
UB SON	1327 (1)	0	1	78.6 (14.7)	–	–
UB HN	371 (0,3)	0	1	79 (10.5)	–	–
In situ carcinoma	186 (9.1)	1 (1)	0.124	73.4 (12.4)	57	0.188

Values in bold highlight statistically significant difference.
HN, haematological neoplasm; SON, solid organ neoplasm; UB, uncertain behaviour.

Table 3 Difference in solid organ neoplasm-related deaths for patients with SLE and the general Spanish population by lineage

	Neoplasm-related deaths n (%)			
	Non-SLE	**SLE**	**P value**	**OR (95% CI)***
Solid organ neoplasm	127 080 (91.1)	73 (80.2)	**0.001**	**0.393 (0.234 to 0.660)**
Malign solid organ neoplasm	124 831 (89.5)	72 (79.1)	**0.003**	**0.432 (0.260 to 0.720)**
Digestive system	415 778 (29.8)	13 (14.3)	**0.001**	**0.423 (0.240 to 0.747)**
Gastrointestinal tract	24 573 (17.6)	5 (5.5)	**0.003**	**0.318 (0.129 to 0.784)**
Oesophagus	2320 (1.7)	1 (1.1)	1	0.785 (0.109 to 5.669)
Stomach	6426 (4.6)	3 (3.3)	0.801	0.764 (0.242 to 2.417)
Small bowel	459 (0.3)	0	1	–
Colorectal	15 062 (10.8)	1 (1.1)	**0.001**	**0.110 (0.015 to 0.789)**
Others	306 (0.2)	0	1	–
Hepato-biliary-pancreas	17 005 (12.2)	8 (8.8)	0.422	0.709 (0.342 to 1.470)
HCC and others	3815 (2.7)	2 (2.2)	1	0.906 (0.217 to 3.781)
Pancreas	8708 (6.2)	3 (3.3)	0.381	0.491 (0.155 to 1.553)
Cholangiocarcinoma	4482 (3.2)	3 (3.3)	0.769	1.109 (0.350 to 3.514)
Lung	25 886 (18.6)	17 (18.7)	1	1.204 (0.698 to 2.0760
Breast	3630 (2.6)	2 (2.2)	1	0.449 (0.109 to 1.847)
Gynaecological	4131 (3)	8 (8.8)	**0.006**	**3.039 (0.145 to 6.307)**
Vulva	279 (0.2)	2 (2.2)	**0.015**	**14.767 (3.587 to 60.792)**
Vagina	63 (0.1)	0	1	–
Cervical	648 (0.5)	3 (3.3)	**0.009**	**3.809 (1.182 to 12.272)**
Uterus	1263 (0.9)	1 (1.1)	0.496	0.990 (0.137 to 7.168)
Ovarian	1747 (1.3)	2 (2.2)	0.316	1.031 (0.251 to 4.236)
Other	131 (0.1)	0	1	–
Otorhinolaryngological	4104 (2.9)	5 (5.5)	0.197	2.183 (0.875 to 5.446)
Endocrine	1782 (1.3)	0	0.634	–
Thyroid	329 (0.3)	0	1	–
Neuroendocrine	1291 (0.9)	0	1	–
Skin	1025 (0.7)	1 (1.1)	0.489	1.665 (0.232 to 11.978)
Melanoma	532 (0.4)	0	1	–
Central nervous system	4029 (2.9)	2 (2.2)	1	0.611 (0.150 to 2.497)
Urological	11 069 (7.9)	5 (5.5)	0.558	1.125 (0.447 to 2.831)
Prostate	3289 (2.4)	1 (1.1)	0.728	0.982 (0.132 to 7.325)
Kidney	2136 (1.5)	2 (2.2)	0.407	1.580 (0.389 to 6.426)
Bladder	5147 (3.7)	2 (2.2)	0.777	0.965 (0.235 to 3.970)
Others	497 (0.4)	0	1	–
Others	4.212 (3)	3 (3.3)	0.756	1.005 (0.318 to 3.179)
Metastasis from unknown/unspecified origin	23 385 (16.8)	16 (17.6)	0.780	0.864 (0.501 to 1.488)
Benign solid organ neoplasm	727 (0.5)	0	0.596	–
Unknown behaviour solid organ neoplasm	1327 (1)	0	1	–
Carcinoma in situ	186 (9.1)	1 (1)	0.124	–

Values in bold highlight statistically significant difference.
*After adjustment for age, sex, alcohol and tobacco consumption.
HCC, hepatocellular carcinoma.

Table 4 Differences in haematological neoplasm-related deaths for patients with SLE and the general Spanish population by lineage

	Neoplasm-related deaths n (%)			
	Non-SLE	**SLE**	**P value**	**OR (95% CI)***
Haematological	12 360 (8.9)	18 (19.8)	**0.001**	**2.546 (1.514 to 4.281)**
Malign haematological	11 989 (8.6)	18 (19.8)	**0.001**	**2.612 (1.554 to 4.392)**
Lymphoma	4237 (3)	11 (12.1)	**<0.001**	**4.208 (2.235 to 7.922)**
Hodgkin's lymphoma	260 (0.2)	1 (1)	0.157	5.752 (0.796 to 41.580)
Non-Hodgkin's lymphoma	3977 (2.9)	10 (11)	**<0.001**	**4.060 (2.100 to 7.849)**
B cell lineage	3537 (2.5)	9 (9.9)	**0.001**	**4.133 (2.071 to 8.246)**
T/NK cell lineage	441 (0.3)	1 (1)	0.269	3.064 (0.425 to 22.070)
Leukaemia	4625 (3.3)	6 (6.6)	0.129	1.940 (0.845 to 4.454)
Myeloid lineage	3191 (2.3)	4 (4.4)	0.293	1.916 (0.702 to 5.233)
Lymphoid lineage	1004 (0.7)	2 (2.2)	0.140	2.664 (0.652 to 10.874)
Multiple myeloma	2165 (1.6)	0	0.409	–
Myelodisplastic syndrome	886 (0.6)	0	1	–
Others	76 (0.1)	1 (1.1)	0.049	–
Unknown behaviour	371 (0.3)	0	1	–
Myeloproliferative disorders	243 (0.2)	0	1	–
Others	128 (0.1)	0	1	–

Values in bold highlight statistically significant difference.
*After adjustment for age, sex, alcohol and tobacco consumption.

Finally, no significant differences between patients with SLE and general Spanish population were found for other SON lineage death rates or risk, including lung (18.7% vs 18.6%, p=1, OR 1.204, 95% CI 0.698 to 2.076), breast (2.2% vs 2.6%, p=1, OR 0.449, 95% CI 0.109 to 1.847), otorhinolaryngological (5.5% vs 2.9%, p=0.197, OR 2.183, 95% CI 0.875 to 5.446), endocrine (0% vs 1.3%, p=0.634), skin (0.7% vs 1.1%, p=0.489, OR 1.665, 95% CI 0.232 to 11.978), central nervous system (2.2% vs

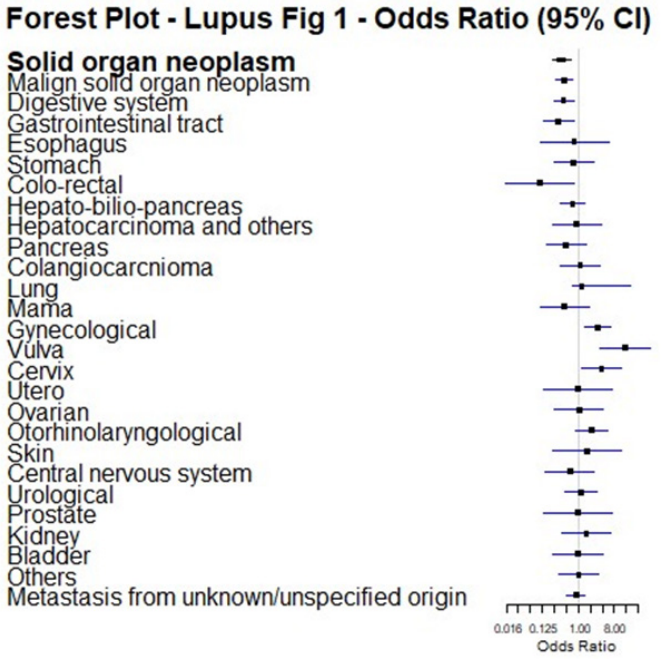

Figure 1 Solid organ neoplasms-related deaths for patients with SLE. The figure represents the risk of dying from solid organ neoplasms for patients with SLE, after adjustment for age, sex, alcohol and tobacco consumption, for each neoplasm lineage. The results are expressed in OR (dots) and 95% CI (bars).

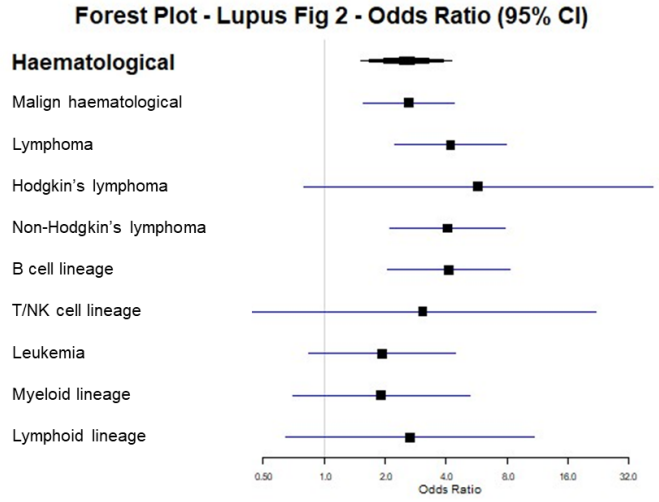

Figure 2 Haematological neoplasms-related deaths for patients with SLE. The figure represents the risk of dying from haematological neoplasms for patients with SLE, after adjustment for age, sex, alcohol and tobacco consumption, for each neoplasm lineage. The results are expressed in OR (dots) and 95% CI (bars). NK, natural killer.

2.9%, p=1, OR 0.611, 95% CI 0.150 to 2.497), urological (5.5% vs 7.9%, p=1, OR 1.125, 95% CI 0.447 to 2.831), other SON (3.3% vs 3%, p=0.756, OR 1.005, 95% CI 0.318 to 3.179) or metastases from unknown or unspecified origin (17.6% vs 16.8%, p=0.780, OR 0.864, 95% CI 0.501 to 1.488).

Haematological neoplasms

The adjusted multivariate analysis confirmed that the risk of dying from HN among patients dying from cancer was higher in patients with SLE (19.8% vs 8.9%, p<0.001), (OR 2.546, 95% CI 1.514 to 4.281). This difference was attributable to the higher proportion of deaths due to non-Hodgkin's lymphoma (11% vs 2.9%, p<0.001, OR 4.060, 95% CI 2.100 to 7.849) and B cell lineage (9.9% vs 2.5%, p=0.001, OR 4.133, 95% CI 2.071 to 8.246), since no differences related to leukaemia (6.6% vs 3.3%, p=0.129, OR 1.940, 95% CI 0.845 to 4.454), multiple myeloma (0% vs 1.6%, p=0.409), MDS (0% vs 0.6%, p=1) or myeloproliferative disorders (0% vs 0.2%, p=1), among others, were found (table 4, figure 2). Moreover, no differences in the mean age of the deceased for each haematological neoplasm lineage were identified, including lymphoma (70.5 vs 70.6 years, p=0.969), non-Hodgkin's lymphoma (71.1 vs 71 years, p=0.976) or B cell lineage non-Hodgkin's lymphoma (70 vs 71.6 years, p=0.765).

DISCUSSION

This large nationwide epidemiological study analyses the differences in mortality from the distinct neoplasm lineages between patients with SLE and the general Spanish population. Herein, we show that patients with SLE dying from cancer present a significantly higher risk of dying from vulvar neoplasms and cervical carcinomas in addition to haematological malignancies and B cell non-Hodgkin's lymphoma, than matched-controls.

In our population, 12.3% of patients with SLE died from neoplasm, a higher rate than previously identified in other cohorts but otherwise lower than the general Spanish population.[3 4 15] On the one hand, our study analysed long-term mortality in all Spanish patients with SLE who were selected from tertiary or specialised centres and from local, non-specialised hospitals and departments/wards. Furthermore, we determined that the neoplasm death risk, which has shown to be indeed high even in the young aged patients with SLE, rises significantly years after disease onset, therefore being a long-term complication of the disease alongside cardiovascular disease.[4 9 21 22] Accordingly, the mean age of the patients with SLE who died from neoplasms in our study was 65 years, many years after the characteristic age of lupus onset or highest activity.[1 2 4] On the other hand, patients with SLE, who died 5 years younger than the general Spanish population, presented a lower rate of mortality from neoplasm. Similarly, other authors have not been able to confirm an overall cancer standardised mortality ratio in patients with SLE, probably because of premature death associated with lupus activity, infection and cardiovascular disease in addition to neoplasms.[3 16 23] Nevertheless, these studies, in parallel to ours, point out that the neoplasm risk among patients with SLE significantly differs depending on the type or neoplasm lineage.

First, HN were responsible for 2.5% of deaths in patients with SLE. Therefore, the risk of dying of cancer was 2.5-fold higher in patients with lupus after adjustment, mostly related to non-Hodgkin's lymphoma of B cell lineage. Previous reports have shown a 1.5 times to 3 times increased risk of haematological malignancies, non-Hodgkin's lymphoma or diffuse large B cell lymphoma incidence in this population.[3 12 20 24–27] However, there is a lack of data regarding their impact on SLE mortality.[3 16 23] Our nationwide study therefore determines and quantifies the excess mortality from haematological malignancies in patients with SLE.

Our research indicated that patients with SLE presented a different mortality rate and risk of digestive or colorectal carcinoma and of gynaecological neoplasms, including vulvar and cervical cancer. While others have described a lower incidence of certain hormone-sensitive tumours such as breast and prostate cancer, to our knowledge there exists no data regarding different rates of colorectal carcinoma risk or mortality in patients with SLE.[13 26 27] In our study, patients with SLE presented a significantly lower death risk from colorectal carcinoma, this in turn being responsible for the lower rate of deaths from digestive neoplasm identified in this population. It seems that universal general colorectal carcinoma screening in the Spanish National Health System led to a prompt detection and treatment of polyps and colorectal carcinoma in patients who are closely followed in the outpatient clinic. Accordingly, the only patient with SLE in Spain who died from colorectal carcinoma was 48 years of age, 2 years younger than when routine screening is recommended.[28]

Finally, our study shows that patients with SLE dying from neoplasms present a threefold mortality risk from gynaecological neoplasms, after adjustment, than the general population. Interestingly, this difference was attributable to cervical carcinomas and vulvar neoplasms. Together, both conditions count for >5% of all the deaths from neoplasm in patients with SLE, again confirming that the higher incidence of these gynaecological neoplasms previously identified in other cohorts is reflected in a higher mortality rate when compared with the general population.[12 13 20 24 26 27] However, it should be highlighted that the mortality rates revealed in our study surpassed the previously identified incidence of these neoplasm, probably because cancer prognosis and progression is worse in an immunosuppressed and comorbid patient such as those who present long-term SLE.[29]

Altogether, we believe our findings emphasise the importance of the detection and subsequent avoidance of cancer risk factors, the universal implementation and improvement of the adherence to certain screening programmes as well as the need to investigate and consider specific early detection and

management programmes in patients with SLE. First, previous studies have already identified cancer risk factors in SLE.[11 21 22 30–32] A large inception SLE cohort published in 2021 identified that disease activity, as well as certain immunosuppressants, such as cyclophosphamide for haematological cancer, in addition to tobacco or age, were related to a higher cancer risk. Similarly, the RELESSER (Lupus Register of the Spanish Society of Rheumatology) cohort identified that a higher Systemic Lupus International Collaborative Clinics/American College of Rheumatology Damage Index, splenomegaly, haemolytic anaemia, vasculitis and pericarditis, among others, were factors related to lymphoma in SLE. Both reports, supported by other studies, confirmed that hydroxychloroquine treatment might confer protection against cancer in patients with SLE.[32 33] On the other hand, our results regarding gynaecological neoplasm confirm that patients with SLE should undertake a specific vulvar and cervical cancer prevention and detection programme. Since cervical cancer, strongly associated with human papillomavirus (HPV) infection, has clearly been shown in several reports to be more frequent and probably more aggressive in patients with SLE, the latest EULAR guidelines confirm that patients with SLE should receive vaccinations against HPV in accordance with the recommendations for the general population.[11–13 20 24 26 27 34–36] In addition, in this setting, the low risk of the onset of autoimmune diseases after vaccination seems to be outweighed by its benefit, particularly in this high-risk population. Similarly, cervical cancer screening by cytology, following clinical guidelines, seems to be highly recommended for patients with SLE according to our results.[34 37–39] In parallel, and in order to ameliorate the impact of vulvar cancer mortality in this setting, specific gynaecological surveillance should be more carefully considered and instigated in patients with SLE. Finally, the management of patients with SLE and their follow-up should consider these issues and should pursue its adherence, whose importance has previously been highlighted.[35 40–42]

Several limitations of this study have to be considered. First, important information regarding disease course (early vs late disease), the use, doses and duration of glucocorticoids, immunosuppressive drugs and antimalarials was not available and could have provided more solid conclusions. Second, this analysis was restricted to hospital admissions, with the resultant limitation in power and the potential selection bias. However, we mainly evaluated categorical variables such as deaths from neoplasm, which are difficult to misclassify. Third, the prevalence of SLE 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. Hence, deaths from neoplasm type or lineage in patients with SLE and the general Spanish population were compared in terms of deaths from neoplasm, giving an estimated proportion and death risk and not an absolute risk ratio. This type of analysis might produce slight variations in the death risk from each neoplasm type in patients with SLE. Thus, and despite the previous reservations, we believe that our study forms a nationwide analysis of a large sample size and for a long study period, yields consistent results which confirm those seen in smaller studies and evaluates a robust outcome such as mortality and not incidence.

In conclusion, patients with SLE present a higher risk of death from vulvar neoplasms, cervical carcinomas and B-cell non-Hodgkin's lymphoma in comparison with the general Spanish population. In addition to developing strategies that might help to attenuate their occurrence and impact, such as decreasing the immunosuppressive burden, specific early detection programmes for these conditions should be investigated and considered carefully.

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Supplementary table 1. Neoplasm related deaths in the Spanish population in the period 2016-2019.

			N (%)	Female (%)	Mean age (years) (SD)
Total			139,531	53,330 (38.2)	70.7 (13,5)
SON			127,153 (91.1)	47,965 (37.7)	70.6 (13,3)
HN			12,378 (8.9)	5,365 (43,3)	71.9 (15,5)
	Malign neoplasm		136,882 (98.1)	52,136 (38.1)	70.6 (13.5)
		Malign SON	124,903 (89.5)	46,951 (37.6)	70.5 (13.3)
		Malign HN	11,979 (8.6)	5,196 (43.3)	71.6 (15.6)
	Solid organ benign		727 (0.5)	370 (50.9)	72.3 (13.5)
	Uncertain behavior		1,698 (1.2)	739 (43.5)	78.7 (13.8)
		UB SON	1,327 (1)	570 (43)	78.6 (14.7)
		UB HN	371 (0.3)	169 (45.6)	79.2 (10.5)
	In situ carcinoma		196 (0.1)	74 (37.8)	72.4 (13.1)

SD: Standard deviation, SON: Solid organ neoplasm, HN: Haematological neoplasm, UB: Uncertain behaviour.