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Impact of immunosuppression on *Listeria monocytogenes* infection in Spain

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ABSTRACT

Introduction: Immunosuppression (IS) determines a higher risk of disease severity from *Listeria monocytogenes* (LM) infection.

Methods: We examined the epidemiology of IS in all patients hospitalized with LM in Spain from 2000 to 2021 in the National Registry of Hospital Discharges. IS was defined by liver disease (LD), diabetes mellitus (DM), chronic kidney disease (CKD), solid organ transplantation (SOT), bone marrow transplantation (BMT), primary immunodeficiencies (ID), systemic autoimmune diseases (SAD), solid organ neoplasms (SON), and hematological neoplasms (HN).

Results: Among 8,152 admissions with LM, 48% were IS. There was an increase from 39.5% to 60% during the study period, mainly driven by rises in DM (from 12.6% to 26.2%), SON (from 9.9% to 17.5%), CKD (from 4.4% to 16.3%), HN (from 6.6% to 13.4%), and LD (from 4.9% to 6.6%) ($p < 0.001$ for all trends). IS fatality rate was higher than in non-IS (22.4% vs 11.3%; OR = 2.09). The proportion of LM patients with IS among LM in-hospital deaths increased from 57.1% in 2000 to 67.95% in 2021 ($p < 0.001$). Fatality risk differed according to baseline IS condition: LD (OR = 2.42), CKD (OR = 1.49), SON (OR 3.01) and HN (OR 1.45).

Conclusions: The prevalence of IS among patients hospitalized with LM in Spain has risen over the past two decades, with a growing impact on fatality rates. These findings should prompt further efforts to prevent and manage properly LM infection.

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Listeriosis; fatality rate; immunosuppressed patients; diabetes mellitus; solid organ neoplasm; hematological neoplasm; chronic kidney disease; liver disease

Introduction

Listeriosis is a zoonotic infectious disease caused by *Listeria* spp., with *L. monocytogenes* (LM) being the primary pathogenic species [1]. *Listeria* is a gram-positive bacillus and a foodborne pathogen, causing sporadic cases and major epidemic outbreaks from contaminated food [2].

Listeriosis presents with a wide spectrum of clinical manifestations, ranging from self-limited febrile gastroenteritis to serious and invasive infections, which can be complicated by bacteremia, sepsis, meningitis, and endocarditis [1,3,4]. Invasive clinical forms are particularly frequent in certain high-risk populations, such as the elderly, immunosuppressed (IS) patients, pregnant women, unborn fetuses, and newborns. Despite its relatively low prevalence, listeriosis poses a significant global health threat due to its high fatality rate in these vulnerable groups [1,2].

In Spain, as in many other European countries, the incidence of listeriosis has steadily increased since the 2000s, despite its designation as mandatory notifiable disease in 2015, following European Commission regulations [5–7]. In parallel, increased fatality rates for LM

have been noticed among the most vulnerable populations, such as the elderly and IS patients. These trends run in parallel with a significant population aging in Spain and a higher prevalence of chronic diseases such as diabetes mellitus, chronic kidney disease and neoplasms [8]. Both factors contribute to a greater impact of listeriosis on these at-risk individuals.

Despite these facts, current data on LM in IS patients, including the main underlying conditions or etiologies, are outdated [2,9–11]. Herein, we aimed to exam the impact, epidemiology, and causes of IS in patients hospitalized with LM in Spain over the last two decades.

Methods

We performed a descriptive analysis based on the Spanish National Hospital Discharge Database (SNHDD). This publicly accessible registry, maintained by the Spanish Government, contains demographic, epidemiological and clinical information regarding hospital admissions nationwide. Clinical information is described along with 14–20 discharge diagnoses codified by the International Classification of Diseases

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(ICD). From 1997 to 2015, the ninth version (ICD-9) was used, and since 2016, the tenth version (ICD-10). This registry has proven valuable for evaluating the burden, epidemiology and time trends of different conditions due to its robustness and nationwide scope [12–14]. This study complements and aligns with our previous findings on *Listeria* epidemiology in Spain, focusing on the subset of patients with IS [15].

Study population

We retrieved all hospital admissions of patients with *Listeria* infection from 2000 to 2021, using ICD-9 code 027.0 and ICD-10 code A32 [15]. Within this population, patients with IS were identified according to any of the following conditions: liver disease (LD), diabetes mellitus (DM), chronic kidney disease (CKD), human immunodeficiency virus (HIV) infection, solid organ transplantation (SOT), bone marrow transplantation (BMT), any primary immunodeficiency (ID), any systemic autoimmune disease (SAD), solid organ neoplasm (SON) and hematological neoplasm (HN). Following the same approach, distinct listeriosis clinical forms were grouped as sepsis, meningoen­cephalitis, endocarditis, and arteritis.

Statistical analysis

We performed a descriptive analysis of the incidence and fatality of LM infection in IS patients hospitalized in Spain between 2000 and 2022. Categorical variables were reported as frequencies and percentages, while numerical variables were presented as mean and standard deviation. The significance of differences between groups was determined using the Pearson chi-square or Student's t-test, as appropriate.

Two binary logistic regression analysis were performed to determine the impact of immunosuppression and its different causes on listeriosis fatality. We selected older age (>65 years-old), clinical forms of listeriosis (sepsis, meningoen­cephalitis, endocarditis and neonatal listeriosis), and immunosuppression as study variables, with fatality as the outcome. In a second step, LD, DM, CKD, HIV, SOT, BMT, ID, SAD, SON and HN were included for adjustment.

Finally, epidemiological trends in hospital admissions and fatality among IS individuals were analyzed over the study period. The linear-by-linear trend test was used to analyze the prevalence and impact of IS and its different etiologies on LM in-hospital fatality rate over the years.

Only values below 0.05 for statistical significance were used in all analyses. All statistical analyses were performed using SPSS version 26.0 (IBM, Madrid, Spain).

Ethics

The study complies with the Declaration of Helsinki and was approved by the Universidad Internacional de La Rioja (UNIR) Ethics Committee (ref. PI: 035/2024). Data were provided anonymously, with all potential patient identifiers removed. In accordance with Spanish law, informed consent was not required for this study.

Results

During the 22-year study period, a total of 8,152 hospital admissions with a diagnosis of *Listeria* were identified in Spain, as described elsewhere [15]. Among them, 3,916 (48%) were reported in patients with IS (Table 1). This group included patients with LD (12.4%), DM (40.4%), CKD (20.2%), HIV infection (1.3%), SOT (1.7%), BMT (1.5%), primary ID (2.7%), SAD (6%), SON (30.9%) and HN (19.3%) (Figure 1). Overall, 2,548 (65.1%) were male, with a mean age of 68.2 years. Only 3 (0.1%) pregnant women were identified. The major clinical forms of listeriosis in patients with IS were sepsis (14.5%), meningoen­cephalitis (31.1%), endocarditis (0.7%), and arteritis (7.4%). The 4,236 non-IS patients admitted with LM were younger (mean age 51.4 years), less frequently male (52.4%) and with a lower rate of sepsis (9.3%) than those with any IS condition ($p < 0.001$).

A total of 878 patients with LM and IS died during admission, resulting in an in-hospital fatality rate higher than that for non-IS patients (22.4% vs 11.3%; $p < 0.001$). After adjustment, IS was independently associated with fatality (OR = 2.09; 95% CI: 1.84–2.38) (Figure 2). In other words, up to 64.7% of the deceased patients with *Listeria* had at least one baseline IS condition.

Differences between the different baseline is conditions

Several differences were identified when each baseline IS condition was analyzed (Table 2). First, individuals with LD, HIV, SOT, BMT, primary ID, SON and HN had lower mean age at admission than the remaining IS causes ($p < 0.001$). Patients with LD were more frequently male (80.6%) and presented a lower rate of meningoen­cephalitis (25.6%) ($p < 0.005$ for both). In contrast, diabetic individuals were older (71.5 years), with a higher proportion of males (67.1%) and a higher rate of meningoen­cephalitis (34.5%) ($p < 0.02$). Patients with CKD were also older (73.8) and presented more sepsis (19.1%) but fewer meningoen­cephalitis (23.6%) than the rest. When all IS causes were evaluated in a multivariate model, LD (OR = 2.42, 95% CI 1.75–3.33), CKD (OR = 1.49, 95% CI 1.23–1.80), SON (OR 3.01, 95% CI 2.59–3.5) and HN

Table 1. Main characteristics of the study population.

Variable	No.
IS patients (N, %)	3,916
Age (years, mean, SD)	68.2 (13.8)
Male (n, %)	2,548 (65.1)
Baseline IS condition (n, %)	
LD (n, %)	485 (12.4)
DM (n, %)	1,582 (40.4)
CKD (n, %)	791 (20.2)
HIV (n, %)	51 (1.3)
SOT (n, %)	68 (1.7)
BMT (n, %)	57 (1.5)
Primary ID (n, %)	104 (2.7)
SAD (n, %)	234 (6)
SON (n, %)	1,209 (30.9)
Advanced/MTX SON (n, %)	751 (19.2)
HN (n, %)	756 (19.3)
Listeria involvement	
Sepsis (n, %)	568 (14.5)
Meningoencephalitis (n, %)	1,218 (31.1)
Endocarditis (n, %)	29 (0.7)
Arteritis (n, %)	289 (7.4)
Outcomes	
Length of admission (days, mean, SD)	19.4 (17.6)
ICU admission (N, %)	215 (14.6)
Length of ICU-admission (days, mean, SD)	10.5 (12.2)
Deaths (N, %)	878 (22.4)

IS: Immunosuppressed, SD: Standard deviation, ICU: Intensive care unit, IS: Immunosuppression, LD: Liver disease, DM: Diabetes mellitus, CKD: Chronic kidney disease, HIV: Human immunodeficiency virus, SOT: Solid organ transplantation, BMT: Bone marrow transplantation, ID: Immunodeficiency, SAD: Systemic autoimmune diseases, SON: Solid organ neoplasm, MTX: Metastatic, HN: Hematological neoplasm.

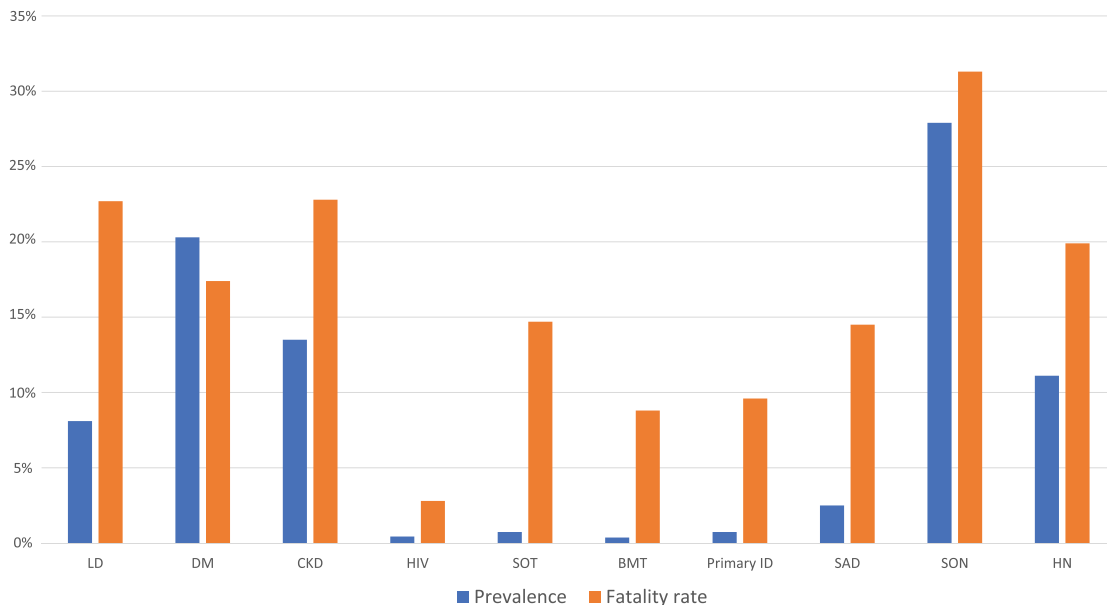


Figure 1. Prevalence and fatality rate of the different baseline conditions determining immunosuppression in admissions with listeriosis in Spain between 1997–2022. LD: Liver disease, DM: Diabetes mellitus, CKD: Chronic kidney disease, HIV: Human immunodeficiency virus, SOT: Solid organ transplantation, BMT: Bone marrow transplantation, ID: Immunodeficiency, SAD: Systemic autoimmune diseases, SON: Solid organ neoplasm, HN: Hematological neoplasm

(OR 1.45, 95% CI 1.19–1.77) were associated with a higher fatality risk after adjustment (Table 3).

Trends in LM admissions in patients with IS

Considering all *Listeria* hospital admissions in Spain between 2000 and 2021, the proportion of patients

with any form of IS rose from 39.5% to 60% ($p < 0.001$). The mean age of these patients increased from 52.5 years in 2000 to 62.2 years in 2021 ($p < 0.001$). During the study period, the fatality rate among patients with IS remained relatively stable (25.8% in 2000 and 22.7% in 2021). However, the proportion of patients with both LM and IS who died

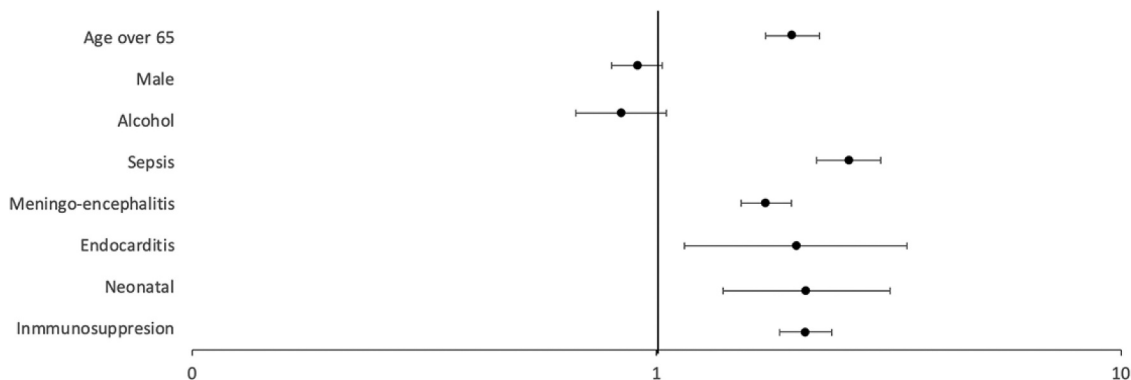


Figure 2. Predictors of fatality in admissions with listeriosis in Spain between 1997–2022. Predictors of in-hospital mortality in listeriosis hospitalized patients. Odds ratio are represented by squares and the lines correspond to 95% confidence interval.

Table 2. Differences between the different baseline is conditions.

	IS patients	LD	DM	CKD	HIV	SOT	BMT	Primary ID	SAD	SON	HN
N (%)	3,916 (48)	485 (12.4)	1,582 (40.4)	791 (20.2)	51 (1.3)	68 (1.7)	57 (1.5)	104 (2.7)	234 (6)	1,209 (30.9)	756 (19.3)
Age (mean, SD)	68.2 (13.8)	62.5 (11.8)	71.5 (11.4)	73.8 (12.5)	50.5 (12.1)	61.3 (12.5)	55.3 (13.4)	59.8 (19.8)	67.6 (14)	67 (12.5)	66.8 (15.6)
Male (n, %)	2,548 (65.1)	391 (80.6)	1,062 (67.1)	519 (65.6)	33 (64.7)	45 (66.2)	30 (52.6)	63 (60.6)	130 (55.6)	801 (66.3)	477 (63.1)
Listeria involvement (n, %)											
Sepsis	599 (15.3)	87 (17.9)	229 (14.5)	151 (19.1)	13 (25.5)	13 (19.1)	11 (19.3)	15 (14.4)	38 (16.2)	190 (15.7)	123 (16.3)
Meningoencephalitis	1,218 (31.1)	124 (25.6)	546 (34.5)	187 (23.6)	21 (39.6)	18 (26.5)	17 (29.8)	47 (45.2)	77 (32.9)	328 (27.1)	213 (28.2)
Endocarditis	29 (0.7)	6 (1.2)	16 (1)	7 (0.9)	0	1 (3.4)	0	0	4 (1.7)	2 (0.2)	1 (0.1)
Arteritis	289 (7.4)	44 (9.1)	127 (8)	84 (10.6)	6 (11.8)	4 (5.9)	6 (10.5)	12 (11.5)	6 (14)	82 (6.8)	57 (7.5)
Outcomes											
Length of admission (days, mean, SD)	19.4 (17.6)	20.5 (15.2)	19.4 (16.6)	18.7 (17.6)	17.6 (12.5)	19 (12.4)	22.1 (24)	22.1 (14.2)	22.1 (20.4)	17.8 (18.40)	19.9 (17.7)
Deaths (n, %)	878 (22.4)	110 (22.7)	275 (17.4)	180 (22.8)	5 (9.8)	10 (14.7)	5 (8.8)	10 (9.6)	34 (14.5)	379 (31.1)	151 (20)

Bold highlights statistical significance ($p < 0.05$). IS: Immunosuppressed, SD: Standard deviation, ICU: Intensive care unit, IS: Immunosuppression, LD: Liver disease, DM: Diabetes mellitus, CKD: Chronic kidney disease, HIV: Human immunodeficiency virus, SOT: Solid organ transplantation, BMT: Bone marrow transplantation, ID: Immunodeficiency, SAD: Systemic autoimmune diseases, SON: Solid organ neoplasm, MTX: Metastatic, HN: Hematological neoplasm.

Table 3. Predictors of fatality in immunosuppressed patients with listeriosis in Spain between 1997–2022.

	OR	95% CI
Age over 65	2.36	2.09–2.73
LD	2.42	1.75–3.33
CKD	1.49	1.23–1.80
SON	3.01	2.59–3.50
HN	1.45	1.19–1.77
Sepsis	2.70	2.32–3.15
Meningoencephalitis	1.83	1.61–2.08
Endocarditis	2.24	1.29–3.89

Predictors of in-hospital mortality in immunosuppressed patients. Odds ratio are represented by squares and the lines correspond to 95% confidence interval. Other variables included in the model for adjustment were: Male sex, alcohol, DM, HIV, SOT, BMT, primary ID, SAD and arteritis.

LD: Liver disease, DM: Diabetes mellitus, CKD: Chronic kidney disease, HIV: Human immunodeficiency virus, SOT: Solid organ transplantation, BMT: Bone marrow transplantation, ID: Immunodeficiency, SAD: Systemic autoimmune diseases, SON: Solid organ neoplasm, HN: Hematological neoplasm.

increased significantly, from 57.1% to 67.95% ($p < 0.001$).

Figure 3 illustrates the distribution of the different baseline IS conditions over time. The linear-by-linear trend test confirmed a significant increase in the

prevalence of the five major IS etiologies among patients admitted with LM between 2000 and 2021, as follows: DM (from 12.6% to 26.2%), SON (from 9.9% to 17.5%), HN (from 6.6% to 13.4%), CKD (from 4.4% to 16.3%) and LD (from 4.9% to 6.6%) ($p < 0.001$ for all trends). At the same time, an increased proportion of patients with LM who died during hospital admission suffered from DM (from 21.4% to 28.4%), SON (from 17.9% to 28.4%), CKD (from 3.6% to 22.2%) and LD (from 3.4% to 11.1%) ($p < 0.001$ for all trends). In contrast, it is noteworthy that the rate of HN among deceased patients admitted with LM steadily decreased from 14.3% to 9.9% ($p = 0.01$).

Discussion

This nationwide epidemiological study examines the burden, temporal trends, clinical manifestations and fatality rate of patients with IS admitted with listeriosis in Spain over the last two decades. Our findings highlight that baseline IS is a significant risk factor for both *Listeria* infection and fatality. However, our study

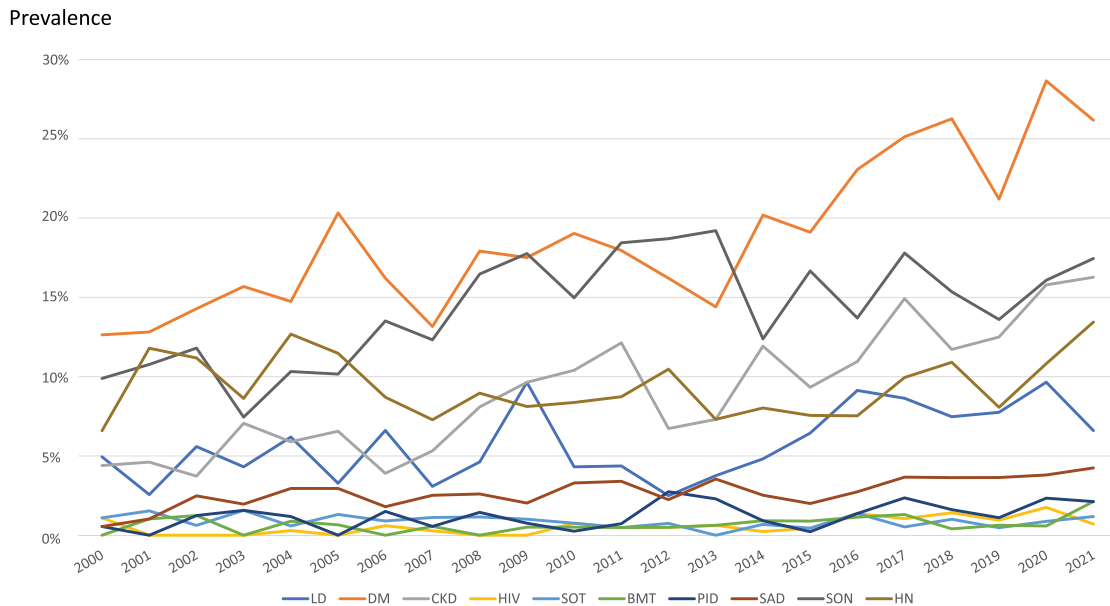


Figure 3. Baseline immunosuppression etiologies in patients hospitalized with listeriosis in Spain between 2000 and 2021. LD: Liver disease, DM: Diabetes mellitus, CKD: Chronic kidney disease, HIV: Human immunodeficiency virus, SOT: Solid organ transplantation, BMT: Bone marrow transplantation, ID: Immunodeficiency, SAD: Systemic autoimmune diseases, SON: Solid organ neoplasm, HN: Hematological neoplasm.

reveals notable differences in listeriosis risk, clinical profiles, disease involvement and prognosis across the distinct IS etiologies.

In previous studies examining the relevance of IS on LM infection, older age and specific comorbidities such as cirrhosis, alcoholism, neoplasms, glucocorticoid therapy, diabetes, cellular immunodeficiencies, and chronic kidney disease, were associated with a higher risk of developing LM infection and poorer clinical outcomes [3,9–11,16–18]. In our study, most systemic or invasive LM infections occurred in patients with IS.

Our nationwide analysis further corroborates that IS entails a two-fold increase in listeriosis-related fatality rate when compared to the general population. Notably, the population of hospitalized IS patients became increasingly older throughout the study period. Therefore, two major risk factors, older age and IS, most likely acted synergically, resulting in a higher proportion of LM admissions and deaths in our study despite the improvements in healthcare and medical management and in the absence of LM significant antibiotic resistance acquiring alongside the study period [19].

The clinical profile and outcome of LM in the hospitalized IS population was very heterogeneous, as highlighted previously [20,21]. Each cause of IS exhibited a distinct pattern of listeriosis involvement. Ultimately, these differences led to varying fatality rates depending on the IS cause. Our study showed that patients with CKD were more susceptible to developing sepsis, while diabetics presented a higher rate of meningococcal meningitis. Conversely, LD and CKD were associated with a lower proportion of meningococcal meningitis

diagnoses. In summary, LD, CKD, SON and HN determined a higher fatality risk in the multivariate analysis. These novel findings add to the body of evidence on LM infection in these at-risk individuals. These differences in listeriosis clinical involvement and prognosis should be considered in the proper management and prevention of LM in these risk populations [22].

Finally, we noticed a changing spectrum of the different baseline IS etiologies over the past twenty years in Spain. Specifically, the prevalence of the major conditions defining immunosuppression (DM, SON, HN, CKD, and LD) have increased in Spain since 2000. This trend was reflected in the increased fatality rate of patients hospitalized with LM in our study. By 2021, up to 60% of patients admitted with LM and more than two-thirds of LM deaths had an underlying IS condition. The only exception was HN, as patients with LM and HN experienced a lower death rate over time, most likely due to advances in hematological therapies and the reduced immunosuppressive effects of newer medications [23]. While these results are not surprising, comprehensive data on the current contribution of LM infection and mortality are scarce [9,11].

Altogether, our findings raise concerns about the impact of IS on LM infection risk and fatality, underscoring the need for targeted programs focused on surveillance and prevention of human listeriosis in the growing population of patients with IS. Furthermore, the alarming fatality rates should encourage physicians to consider early diagnosis and prompt empiric treatment for LM infection in high-risk populations, such as those with IS, even in the absence of epidemic outbreaks.

Several limitations of this study should be acknowledged. First, important information regarding disease course, baseline IS conditions or current immunosuppressants, antimicrobial treatment, origin and setting was unavailable, limiting the ability to draw more robust conclusions. Moreover, specific microbiological data and isolates were not accessible, and therefore, the impact and contribution of certain hyper-virulent species, declared primarily in humans in France, but also in animal reservoirs in Spain, could not be assessed [24,25]. Only microbiologically confirmed cases from discharge reports were included in the SNHDD and therefore retrieved and analyzed. While this approach may yield more reliable results, it may also lead to an underestimation of total cases, as a significant proportion of LM suspected cases were not taken into consideration. Finally, our analysis was restricted to hospital admissions, potentially disregarding clinically mild forms of listeriosis that did not require hospitalization. However, we consider this to be unlikely, given the intrinsic severity and risks associated with LM infection among patients with IS. Despite all these caveats, our study benefits from its nationwide scope, large sample size, and long study period, yielding robust data and consistent results.

In conclusion, the prevalence of LM in patients hospitalized with IS in Spain has significantly risen during the last 20 years. Their fatality rate has also increased. Therefore, efforts to prevent and better manage LM in patients with IS are warranted.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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Data sharing statement

The data proceeds from a public registry from the Spanish National Hospital Discharge Database. All data are freely available. The database from the Spanish Ministry of Health can be accessed upon request. Data are anonymously given.

Patient and Public Involvement. None declared.

Ethical approval information

The study complies with the Declaration of Helsinki and was approved by the local research ethics committee. The data were provided after all potential patient's identifiers had

been deleted, and all data were given anonymously. According to the Spanish law, informed consent was not required for the study.

Abbreviations

BMT	Bone marrow transplantation
CKD	Chronic kidney disease
DM	Diabetes mellitus.
HIV	Human immunodeficiency virus.
HN	Haematological neoplasm.
ICD	International Classification of Diseases
ID	Immunodeficiency
IS	Immunosuppression
LD	Liver disease.
SAD	Systemic autoimmune disease
SNHDD	Spanish National Hospital Discharge Database.
SON	Solid organ neoplasm

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