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Sex differences in clinical characteristics and outcomes in patients hospitalized with cellulitis in Spain (2016-2022)

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ABSTRACT

Purpose: To estimate hospitalization rates, analyze sex-specific clinical characteristics, assess in-hospital mortality and its risk factors, and measure the economic burden of cellulitis hospitalizations.
Materials and Methods: This retrospective population-based study included adults aged ≥15 years hospitalized for cellulitis in Spain from 2016 to 2022. Multivariable logistic regression was used to identify factors associated with in-hospital mortality (IHM).
Results: A total of 194,673 cellulitis hospitalizations were recorded (90,828 women and 103,845 men). The mean hospitalization rates per 1000 admissions and per 100,000 inhabitants were lower in women than men (6.0 vs. 7.6 and 63 vs. 76, respectively). In women, cellulitis was more common in those aged 65-75 and ≥80 years and in those with hypertension, dyslipidemia, heart failure, or hypothyroidism. Women had a higher crude IHM (7.4%) than men (5.9%), but sex was not significantly associated with mortality after adjustment (AOR: 1.02; 95% CI: 0.93-1.07). The strongest predictors of mortality were similar in both women and men. These included leukemia (AOR: 4.45 vs. 3.15), age ≥80 years (AOR: 3.96 vs. 4.39), sepsis (AOR: 3.59 vs. 2.95), neoplasia (AOR: 3.44 vs. 3.47), and cirrhosis (AOR: 2.49 vs. 2.41). The total hospitalization cost for women was €451.8 million, with a median cost of €3,653 per admission.
Conclusions: The clinical profile and outcomes of cellulitis differ by sex. In women, advanced age, comorbidities, and complications like sepsis significantly increased mortality risk.

Introduction

Cellulitis, a common bacterial skin infection, is a significant cause of hospital admissions and healthcare burden globally [1]. It can occur at any age but is most common in middle-aged and older adults [1–3]. Specific risk factors include previous episodes of cellulitis, the presence of wounds or ulcers, tinea pedis, chronic edema/lymphedema, venous insufficiency, excoriating skin diseases, and obesity [1–4]. While its general epidemiology is well-documented, less is known about how incidence, clinical characteristics and outcomes vary between sexes in hospitalized patients [5–8]. Investigating these differences is essential for tailoring clinical management and informing healthcare policies.

Sex-related biological factors, such as hormonal differences, immune responses, and genetic predispositions, may influence the presentation and progression of cellulitis [6,8,9]. Furthermore, these disparities can affect outcomes such as length of hospital stay, complications, and in-hospital mortality [6,9]. Despite this, comprehensive analyses of sex-specific trends in cellulitis-related hospitalizations in Spain and globally remain limited.

To address this gap, we conducted a population-based analysis of cellulitis hospitalizations in Spain from 2016 to 2022. Using administrative hospital records, we estimated hospitalization rates, analyzed sex-specific clinical characteristics, and assessed in-hospital mortality and risk factor, measured the hospitalization cost. By providing detailed insights into these trends, this study aims to improve understanding of the role of sex in cellulitis and support the development of evidence-based approaches to patient care.

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Patients and methods

Study design, data source, and study period

This observational, cross-sectional study analyzed patients diagnosed with cellulitis who were discharged from public hospitals in Spain. The data source was the Spanish Registry of Specialist Care Activities (SRSCA) provided by the Spanish Health Ministry (SHM). This registry includes the Minimum Basic Dataset (MBDS), which contains patients' demographic characteristics, administrative data, and clinical variables related to diagnoses and procedures performed during hospitalization. Diagnoses and procedures were coded according to the International Classification of Diseases, 10th edition (ICD-10) [10]. The SHM conducted periodic audits to ensure registry accuracy.

The data on all hospital admissions for individuals aged 15 years and older between March 1, 2016, and December 31, 2022, were extracted. Data collected included discharge dates and information on cellulitis hospitalizations identified using the ICD-10 code L03.x ["cellulitis and acute lymphangitis"]. This code encompasses cellulitis and acute lymphangitis while excluding: K61.x ["cellulitis of anal and rectal regions"], H60.1 ["cellulitis of external auditory canal"], N76.4 ["cellulitis of external genital organs in female"], N48.2, N49.x ["cellulitis of external genital organs in male"], H00.0 ["cellulitis of eyelid"], H04.3 [cellulitis of eyelid"], K12.2) [cellulitis of mouth"], J34.0 [cellulitis of nose]; L98.3 ["eosinophilic cellulitis or Wells syndrome], L98.2["febrile neutrophilic dermatosis or Sweet syndrome"], L98.2 ["subacute and chronic lymphangitis"]. The code L03.x includes the following specific categories: L03.0 ["cellulitis of finger and toe (infection of nail, onychia, paronychia, perionychia)"], L03.1 ["cellulitis of other parts of limb (axillae, hip, shoulder)"], L03.2 ["cellulitis of face"], L03.3 ["cellulitis of trunk (abdominal wall, back, chest wall, groin, perineum, umbilicus)"], L03.8 ["cellulitis of other sites (head, scalp) except face)"] and (5) L03.9 ["cellulitis, unspecified"]

Variables

We analyzed the following variables: (A) Demographics: age (categorized as 15-64, 65-79, and $\geq$80 years) and sex. (B) Clinical characteristics: Type of cellulitis (classified by ICD-10 codes), comorbidities (e.g., hypertension, diabetes, dyslipidemia, chronic kidney disease, obesity, ischemic heart disease, heart failure, neoplasms, lymphoma, leukemia, cirrhosis, hypothyroidism, human immunodeficiency virus (HIV), organ transplant). (C) Complications: sepsis, severe sepsis, acute kidney failure, and admission to the intensive care unit (ICU). (D) Microbiology: *Escherichia coli* infection, *Streptococcus* sp infection, *Staphylococcus sp*. infection, *Pseudomonas sp*. infection, anaerobes infection. (E) Outcomes: length of hospital stays, type of discharge (home/deceased), and cost of hospitalization. Supplementary Table 1 shows the ICD-10 codes of all clinical entities, comorbidities and microbiology included in the study.

The administrative database does not include standardized criteria such as the Sepsis-3 definitions. Instead, sepsis is identified using two codes: A40.x (*Streptococcal* sepsis), and A41.x (other sepsis, including sepsis due to *Staphylococcus aureus*, other specified or unspecified staphylococci, *Haemophilus influenzae*, anaerobes, other Gram-negative organisms, and other specified or unspecified causes). These codes are commonly used in clinical coding to identify and classify severe systemic infections caused by specific bacteria. Severe sepsis is coded as ICD-10: R65.2, which is defined as infection with associated acute organ dysfunction, sepsis with multiple organ dysfunction, or systemic inflammatory response syndrome due to an infectious process with acute organ dysfunction. Additionally, it is required to code first the underlying infection.

According to the microbiology variable, a coded diagnosis of infection by a microorganism is assumed to indicate that the microorganism was identified in a culture isolate (blood or elsewhere). However, neither the culture result nor the culture site is available. The code A40.x corresponds to *Streptococcal* sepsis, while A41.x refers to other sepsis, *a*nd codes B95 to B97 (bacterial and viral infectious agents) are used as additional codes to identify the infectious agent(s) in diseases classified elsewhere (Supplementary Table 1).

The cost of each hospital stay was calculated using the Diagnosis-Related Groups (DRG) patient classification system. Cost data were derived from the clinical-administrative information in the MBDS and the Analytical Accounting systems of a sample of hospitals, which is reviewed annually [11].

Data analysis

The hospitalization rate (HR) for cellulitis was defined as the number of cellulitis admissions per 100,000 inhabitant per year, using population data from the Spanish Statistics Institute [12]. Additionally, cellulitis admissions per 1000 all-cause admissions per year were calculated using data from the SRSCA - Minimum Basic Dataset [13].

Categorical variables were presented as absolute values and percentages, while continuous variables were summarized as medians and interquartile ranges (IQRs). Normality of the data was assessed with the Kolmogorov-Smirnov test. Statistical comparisons were performed using the chi-square test or Fisher's exact test for categorical variables and the Mann-Whitney U test (for two categories) or Kruskal-Wallis test (for three or more categories) for continuous variables. A P-value of <0.05 was considered statistically significant.

Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated. Multivariable logistic regression was used to identify independent associations of cellulitis-related hospitalizations between sexes and predictors of in-hospital mortality for women and men. Significant categorical variables from the univariate analysis were entered into the multivariate logistic regression model using a stepwise selection method with the likelihood ratio test. Adjusted ORs (AOR) with 95% CIs were calculated. Model fit was evaluated using the area under the receiver operating characteristic curve (AUC) with 95% CIs. All analyses were conducted using IBM SPSS for Windows (version 25.0; IBM Corp., Armonk, NY, USA).

Ethical aspects

The database was provided by the SHM upon request. To ensure patient anonymity, all potential identifiers were removed before analysis. According to Spanish laws, informed consent was not required for this study. The research protocol was approved by the Committee of Ethics and Integrity in Research of Miguel Hernández University (ref. AUT.DMC.JMRR.241103). All procedures adhered to the ethical standards outlined in the revised Declaration of Helsinki (2013)

Results

Annual evolution of absolutes cases and HR by sex

During the study period, there were 28.7 million hospital admissions among adults aged 15 years and older (15.0 million women and 13.9 million men), of which 194,673 were for cellulitis (90,828 in women and 103,845 in men). The number of annual cellulitis admissions increased from 27,074 in 2016 to 29,499 in 2019,

Table 1
Episodes of cellulitis hospitalization, hospitalization rates per 1000 all-cause admissions and per 100,000 inhabitants by age group (15-64, 65-79, >80 years) and sex (women, men, overall population) in Spain

	15-64 y			65-79 y			>80 y			Overall		
Year	N	HR[a]	HR[b]	N	HR[a]	HR[b]	N	HR[a]	HR[b]	N	HR[a]	HR[b]
	Women											
2016	3476	2.9	22	3716	8.1	136	5540	11.2	535	12732	5.9	66
2017	3659	3.0	24	3966	8.4	123	5937	11.3	330	13562	6.1	67
2018	3430	2.9	22	3810	8.0	116	6013	11.4	333	13253	6.0	65
2019	3624	3.0	23	3862	8.0	114	6230	12.0	347	13716	6.2	66
2020	2757	2.6	18	3252	7.7	94	5367	11.4	300	11376	5.8	55
2021	2937	2.6	19	3479	7.5	99	6353	12.8	351	12769	6.1	61
2022	3106	2.7	20	3706	7.5	102	6608	12.2	367	13420	6.2	63
Mean	3267	2.8	21	3677	7.9	111	5993	11.7	360	12953	6.0	63
	Men											
2016	6838	7.7	44	4320	7.1	159	3184	8.0	308	14342	7.6	75
2017	7303	7.9	47	4608	7.3	167	3459	8.2	329	15370	7.8	80
2018	7036	7.7	45	4542	7.0	161	3419	8.0	324	14997	7.5	77
2019	7347	7.9	47	4895	7.5	168	3541	8.4	339	15783	7.8	81
2020	5943	7.1	38	4246	7.1	143	3079	8.1	295	13268	7.3	67
2021	6132	6.8	39	4659	7.4	154	3618	9.1	342	14409	7.4	73
2022	7038	7.9	44	4884	7.2	157	3754	8.6	355	15676	7.8	78
Mean	6785	7.5	43	4588	7.2	158	3429	8.3	327	14811	7.6	76
	Overall population											
2016	10314	5.0	34	8036	7.5	136	8724	9.7	310	27074	6.7	69
2017	10962	5.1	36	8574	7.7	143	9396	9.9	329	28932	6.9	73
2018	10466	4.9	34	8352	7.5	137	9432	9.9	330	28250	6.7	71
2019	10971	5.1	35	8757	7.7	139	9771	10.4	344	29499	7.0	73
2020	8700	4.6	28	7498	7.3	117	8446	9.9	298	24644	6.5	61
2021	9069	4.4	29	8138	7.4	125	9971	11.1	348	27178	6.7	67
2022	10144	5.0	32	8590	7.4	128	10362	10.6	363	29096	7.0	71
Mean	10055	4.9	32	8268	7.5	132	9422	10.2	331	27765	6.8	69

Abbreviations: N, sample size (number of admissions); HR, hospitalization rate; y, year.
[a] Number of hospitalizations for cellulitis per 1000 all-cause admissions per year.
[b] Number of hospitalizations for cellulitis per 100,000 inhabitants per year.

then decreased to 24,644 in 2020, before rising again to 29,096 in 2022. The annual number of cellulitis admissions in both women and men followed a similar decline during the COVID-19 pandemic (Table 1).

The average number of annual admissions was lower in women than in men for patients aged 15-64 years (3,267 vs. 6,785) and 65-79 years (3,677 vs. 4,588), but higher in women for patients aged 80 years and older (5,993 vs. 3,429) (Table 1).

The mean hospitalization rate (HR) in women was lower than in men (6.0 vs. 7.6 per 1,000 admissions per year and 63 vs. 76 per 100,000 inhabitants per year). Among patients aged 15-64 years, women had lower HRs than men (2.8 vs. 7.5 per 1000 admissions per year and 21 vs. 43 per 100,000 inhabitants per year). For patients aged 65-79 years, women had the same HR per 1000 admissions as men (7.9 vs. 7.9) but a lower HR per 100,000 inhabitants (111 vs. 158). In patients aged 80 years and older, women had higher HRs than men (11.7 vs. 8.3 per 1,000 admissions per year and 360 vs. 327 per 100,000 inhabitants per year) (Table 1).

Clinical characteristics stratified by sex

Table 2 summarizes the differences in age, comorbidities, complications, and the clinical course of cellulitis between sexes, while Table 3 provides the unadjusted and adjusted odds ratios (ORs). After multivariate analysis, the characteristics most strongly associated with cellulitis in women included age groups 65-79 years and over 80 years, as well as conditions such as hypertension, dyslipidemia, obesity, heart failure, hypothyroidism, neurodegenerative diseases, and infections caused by *Escherichia coli*.

In contrast, factors less associated with cellulitis in women included cellulitis located on the limbs, toes, and hands, as well as diabetes mellitus, smoking, COPD, chronic renal failure, ischemic heart disease, alcohol abuse, leukemia, neoplasms, cirrhosis, organ transplant, HIV infection, acute kidney failure, ICU admission, and infections caused by streptococcal, staphylococcal, and anaerobic bacteria (Table 3).

Risk factors for mortality in overall population (women and men)

The hospital mortality rate was higher in women compared to men, with rates of 7.4% (6,764/90,828) and 5.9% (6,103/103,845), respectively. This resulted in an unadjusted OR of 1.28 (95% CI: 1.24-1.33; $P < 0.001$). However, after adjusting for variables associated with mortality in the univariate analysis, sex was no longer significantly associated with mortality (AOR: 1.02; 95% CI: 0.93-1.07; $P = 0.2$). Detailed risk factors for mortality in the overall population are presented in Supplementary Table 2. Table 4 presents the multivariate-adjusted analysis of risk factors in the overall population.

Risk factors for mortality among women

Supplementary Table 3 outlines mortality risk factors for women and men, including unadjusted ORs. In the adjusted analysis, clinical locations of cellulitis associated with higher mortality risk in women included cellulitis of the trunk (AOR: 1.49). Comorbidities significantly linked to increased mortality in women were: leukemia (AOR: 4.45), age ≥80 years (AOR: 3.96), neoplasia (AOR: 3.44), cirrhosis (AOR: 2.49), heart failure (AOR: 2.10), lymphoma (AOR: 2.03), age 65-79 years (AOR: 1.96), neurodegenerative disease (AOR: 1.50), ischemic heart disease (AOR: 1.31), chronic renal failure (AOR: 1.32), and diabetes mellitus (AOR: 1.08).

Complications associated with higher mortality included: sepsis (AOR: 3.59), severe sepsis (AOR: 2.60), acute kidney failure (AOR: 2.30), and ICU admission (AOR: 1.89). Conversely, factors associated with lower mortality risk in women were: dyslipidemia (AOR: 0.80), hypothyroidism (AOR: 0.81), hypertension (AOR: 0.91), cellulitis of the hand and feet (AOR: 0.76), and cellulitis of the face

Table 2
General characteristics of cellulitis hospitalizations and gender differences

	Total (N = 194,673)	Women (N = 90,928)	Men (N = 103,845)	*P*-value
Age				
Median (IQR)	72 (67-83)	78 (64-86)	67 (53-79)	**<0.001**
15-64 y	36.3%	25.3%	45.9%	**<0.001**
65-80 y	29.8%	28.4%	31.0%	
>80 y	34.0%	46.3%	23.2%	
Location of cellulitis[a]				
Other parts of limb [L03.1]	77.1%	79.3%	75.2%	**<0.001**
Trunk [L03.3]	9.7%	9.8%	9.7%	0.785
Finger and toe [L03.0]	6.6%	4.3%	8.7%	**<0.001**
Face [L03.2]	3.9%	3.9%	3.9%	0.445
Unspecified [L03.9]	2.5%	2.7%	2.4%	**<0.001**
Other sites [L03.8]	1.2%	1.1%	1.2%	0.052
Comorbidities				
Hypertension	54.9%	60.3%	50.2%	**<0.001**
Diabetes mellitus	31.3%	28.6%	33.6%	**<0.001**
Dyslipidemia	28.5%	29.5%	27.7%	**<0.001**
Heart failure	18.9%	23.4%	14.9%	**<0.001**
Chronic Kidney disease	18.9%	20.7%	17.3%	**<0.001**
Smoking	10.2%	5.0%	14.8%	**<0.001**
Obesity	16.9%	19.9%	14.3%	**<0.001**
Alcohol consumption	6.9%	1.7%	11.5%	**<0.001**
COPD	7.9%	4.0%	11.3%	**<0.001**
Ischemic heart disease	8.8%	6.1%	11.3%	**<0.001**
Neoplasia	8.4%	8.0%	8.8%	**<0.001**
Cirrhosis	3.5%	2.1%	4.6%	**<0.001**
Neurodegenerative disease	6,5%	9.1%	4.2%	**<0.001**
Hypothyroidism	6.4%	10.4%	2.9%	**<0.001**
Lymphoma	2.0%	2.0%	2.0%	0.210
Transplantation	1.3%	0.9%	1.6%	**<0.001**
HIV infection	0.7%	0.3%	1.0	**<0.001**
Leukemia	0.8%	0.8%	0.9%	**0.002**
Clinical Complications				
Acute kidney failure	13.9%	14.8%	13.1%	**<0.001**
Sepsis	6.4%	6.6%	6.3%	**0.002**
Severe sepsis	3.1%	3.2%	3.1%	0.292
Outcome				
Length of stays, median (IQR)	8 (4-14)	7 (4-13)	8 (4-14)	**<0.001**
ICU admission[b]	4.3%	3.5%	5.1%	**<0.001**
Days in ICU, median (IQR)[b]	4 (2-11)	4 (2-10)	5 (2-11)	**0.004**
In-hospital mortality (IHM)	6.6%	7.4%	5.9%	**<0.001**
Days from admission to IHM, median (IQR)	10 (4-19)	9 (4-17)	10 (5-21)	**<0.001**
Microbiology (ICD-10)				
Staphylococcus sp.	10.3%	8.4%	11.9%	**<0.001**
Escherichia coli	4.5%	5.5%	3.7%	**<0.001**
Pseudomonas sp	4.5%	4.7%	4-3%	**<0.001**
Streptococcus sp	4.0%	3.6%	4.3%	**<0.001**
Anaerobes	0.2%	0.2%	0.2%	**0.007**

Abbreviations: COPD, chronic obstructive pulmonary disease; HIV: human immunodeficiency virus; ICD-10, International Classification of Diseases, 10th Revision; ICU, intensive care unit, IQR, interquartile range; IHM, in-hospital mortality.
The values is in percentage for qualitative variables and median with interquartile range (IQR) for quantitative variables In blond p value < 0.05.
[a] ICD code.
[b] Missing value n = 2903 (1472 male /1431 female).

(AOR: 0.77) (table 4). The model's discriminative ability, measured by the AUC, was 0.818 (95% CI: 0.813-0.823; $P < 0.001$).

Risk factors for mortality among men

Supplementary Table 4 presents in-hospital mortality risk factors for men, including unadjusted ORs. In the adjusted analysis (Table 4), many factors were similar to those observed in women, with comparable AORs for cellulitis of the trunk, leukemia, age ≥80 years, neoplasia, cirrhosis, heart failure, lymphoma, age 65-79 years, neurodegenerative disease, ischemic heart disease, chronic renal failure, sepsis, severe sepsis, acute kidney failure, and ICU admission.

Unique to men, COPD was associated with increased in-hospital mortality risk, while diabetes mellitus was not. Factors associated with lower mortality risk in men included: dyslipidaemia, hypertension, cellulitis of the hand and feet. Unlike women, cellulitis of the face and hypothyroidism were not associated with a reduced risk of mortality in men (Table 4). The model's discriminative ability, measured by the AUC, was 0.849 (95% CI: 0.845-0.853; $P < 0.001$).

Economic burden of cellulitis in women and men

Over a seven-year period, the direct costs of 194,673 hospitalizations for cellulitis in the Spanish National Health System (NHS) were estimated at €451.8 million for women and €578.5 million for men. These costs varied significantly across age groups: €116.9 million (women) and €254.9 million (men) in patients aged <65 years, €137.8 million (women) and €198.9 million (men) in those aged 65-79 years, and €196.9 million (women) and €124.7 million (men) in patients aged ≥80 years (Table 5). The average annual cost was €64.4 million for women, which was lower than €82.4 million for men.

Table 3
crude and adjusted odds ratios for sex differences in cellulitis hospitalization (men as reference)

	OR 95% CI)	*P*-value	AOR 95% CI)	*P*-value
Age				
15-64 y	1		1	
65-80 y	1.66 (1.62-1.70)	<0.001	1.64 (1.60-1.69)	**<0.001**
>80 y	3.62 (3.54-3.70)	<0.001	3.16 (3.07-3.25)	**<0.001**
Location of cellulitis (ICD-10)[a]				
Other parts of limb [L03.1]	1.26 (1.23-1.28)	<0.001	0.84 (0.82-0.86)	**<0.001**
Trunk [L03.3]	1.00 (0.97-1.35)	0.785	NI	-
Finger and toe [L03.0]	0.47 (0.45-0.49)	**<0.001**	0.53 (0.50-0.55)	**<0.001**
Face [L03.2]	0.98 (0.94-1.03)	0.445	NI	-
Unspecified [L03.9]	1.13 (1.03-1.20)	**<0.001**	NI	-
Other sites [L03.8]	0.92 (0.84-1.00)	0.052	NI	-
Comorbidities				
Hypertension	1.51 (1.48-1.54)	**<0.001**	1.08 (1.06-1.11)	**<0.001**
Diabetes mellitus	0.70 (0.77-0.86)	**<0.001**	0.73 (0.72-0.75)	**<0.001**
Dyslipidemia	1.09 (1.07-1.11)	**<0.001**	1.00 (0.98-1.03)	0.609
Heart failure	1.74 (1.70-1.78)	**<0.001**	1.36 (1.32-1.40)	**<0.001**
Chronic Kidney disease	1.25 (1.22-1.27)	**<0.001**	0.86 (0.84-0.89)	**<0.001**
Smoking	0.30 (0.29-0.31)	**<0.001**	0.62 (0.59-0.64)	**<0.001**
Obesity	1.48 (1.45-1.52)	**<0.001**	1.73 (1.66-1.77)	**<0.001**
Alcohol consumption	0.13 (0.13-0.14)	**<0.001**	0.22 (0.19-0.21)	**<0.001**
COPD	0.32 (0.31-0.33)	**<0.001**	0.25 (0.24-0.26)	**<0.001**
Ischemic heart disease	0.51 (0.49-5.27)	**<0.001**	0.42 (0.41-0.43)	**<0.001**
Neoplasia	0.89 (0.86-0.92)	**<0.001**	0.90 (0.87-0.94)	**<0.001**
Cirrhosis	0.44 (0.42-0.41)	**<0.001**	0.91 (0.86-0.78)	0.008
Neurodegenerative disease	2.29 (2.20-2.37)	**<0.001**	1.28 (1.33-1.44)	**<0.001**
Hypothyroidism	3.90 (3.74-4.07)	**<0.001**	3.54 (3.39-3.71)	**<0.001**
Lymphoma	0.96 (0.90-1.02)	0.210	NI	-
Transplantation	0.60 (0.55-0,65)	**<0.001**	0.80 (0.74-0.88)	**<0.001**
HIV infection	0.27 (0.24-0.32)	**<0.001**	0.59 (0.51-0.68)	**<0.001**
Leukemia	0.85 (0.77-0.94)	**0.002**	0.86 (0.77-0.96)	**<0.001**
Clinical Complications				
Acute kidney failure	1.15 (1.12-1.18)	**<0.001**	0.88 (0.86-0.91)	**<0.001**
Sepsis	1.06 (1.02-1.10)	**0.002**	1.01 (0.96-1.05)	0.671
Severe sepsis	0.97 (0.23-1.02)	0.292	NI	-
Outcome				
ICU admission	0.67 (0.64-0.71)	**<0.001**	0.85 (0.81-0.90)	**<0.001**
In hospital mortality	1.28 (1.24-1.33)	**<0.001**	1.00 (0.96-1.04)	0.832
Microbiology (ICD-10)				
Staphylococcus sp. Infection	0.68 (0.66-0.70)	**<0.001**	0.77 (0.75-0.80)	**<0.001**
Streptococcus sp. infection	0.81 (0.78-0.56)	**<0.001**	0.93 (0.89-0.98)	**0.016**
Pseudomonas sp infection	1.10 (1.05-1.14)	**<0.001**	1.01 (0.96-1.63)	0.595
Escherichia coli infection	1.53 (1.47-1.60)	**<0.001**	1.42 (1.36-1.50)	**<0.001**
Anaerobe infection	0.75 (0.61-0.93)	**0.007**	0.74 (0.59-0.93)	**0.011**

Abbreviations: COPD, chronic obstructive pulmonary disease; HIV: human immunodeficiency virus; ICD-10, International Classification of Diseases, 10th Revision; ICU, intensive care unit; NI, non-included in the multivariable analysis due to p value > 0.05 or nor clinically relevant; y, year. In blond *P* value < 0.05.
[a] ICD-10 code.

The median cost per hospitalization was also lower in women (€3,653) compared to men (€3,669; $P < 0.001$). This difference persisted across age groups: €3,560 (women) vs. €3,585 (men) for patients aged <65 years, €3,233 (women) vs. €4,178 (men) in the 65-79 years age group, and €3,698 (women) vs. €3,996 (men) for those aged ≥80 years (Table 5).

Supplementary Table 5 presents the economic burden of cellulitis hospitalizations stratified by sex, age group, and year. The annual costs increased from 2016 to 2022, rising from €61.4 million to €70.6 million in women and from €77.3 million to €91.8 million in men. Similarly, the median cost per hospitalization increased during this period, from €3,222 to €3,700 in women and from €3,342 to €3,793 in men. Notably, the median cost was higher during the COVID-19 pandemic years of 2020 and 2021, reaching €4,206 and €4,208 for women, and €5,569 and €4,524 for men, respectively.

Discussion

This study outlines the epidemiological and clinical profile of patients hospitalized with cellulitis in Spain, stratified by sex, using data from an administrative database. Hospitalization rates remained stable throughout the study period, except for a decrease during the COVID-19 pandemic. Women had lower hospitalization rates than men, except in the group aged 80 years and older. Mortality rates were similar between sexes after adjusting for variables. Risk factors for mortality included age, comorbidities, and disease severity. The economic cost associated with hospitalization was lower for women.

Reports on the incidence of skin and soft tissue infections are scarce [7]. In the USA, data from 1997 to 2007 indicate rising hospitalizations linked to MRSA [14], with rates stabilizing from 2005 to 2010. Our study observed a relatively stable admission rate over six years, with a slight decrease during the COVID-19 peak, consistent with pandemic-related shifts in admission patterns [15–16]. These hospitalization rates are not directly comparable to those of other countries due to differences in hospital admission criteria.

In 1999, 176 episodes met the case definition of lower-extremity cellulitis in Olmsted County, resulting in an incidence rate of 199 per 100,000 person-years. The sex-specific incidence for all cases of lower-extremity cellulitis (both admitted and nonadmitted patients, with a ratio of 1:5) was 197 per 100,000 person-years for women and 201 per 100,000 person-years for men [6,7]. In our

Table 4
Adjusted odds ratios for hospital mortality in women, men, and the overall population with cellulitis hospitalization

	Women		Men		Overall	
	AOR 95% CI)	p-value	AOR 95% CI)	*P*-value	AOR 95% CI)	*P*-value
Sex						0.239
Men	NI		NI		1	
Women	NI		NI		1.02 (0.93-1.070)	
Age						
15-64 y	1		1		1	
65-80y	1.95 (1.76-2.17)	**<0.001**	2.07 (1.91-2.26)	**<0.001**	2.03 (1.90-2.18)	**<0.001**
>80 y	3.96 (3.57-4.40)	**<0.001**	4.39 (4.03-4.79)	**<0.001**	4.21 (3.94-4.49)	**<0.001**
Location of cellulitis (ICD-10)[a]						
Other parts of limb [L03.1]	NI		NI		NI	
Trunk [L03.3]	1.49 (1.36-1.63)	**<0.001**	1.23 (1.13-1.35)	**<0.001**	1.36 (1.28-1.56)	**<0.001**
Finger and toe [L03.0]	0.76 (0.63-0.91)	**0.033**	0.69 (0.61-0.82)	**<0.001**	0.73 (0.65-0.81)	**<0.001**
Face [L03.2]	0.77 (0.62-0.95)	**0.018**	0.95 (0.79-1.13)	0.575	0.87 (0.76-1.00)	0.053
Unspecified [L03.9]	NI	-	NI	-	NI	
Other sites [L03.8]	NI	-	NI	-	NI	
Comorbidities						
Hypertension	0.91 (0.85-0.97)	**0.006**	0.80 (0.75-0.86)	**<0.001**	0.85 (0.81-0.89)	**<0.001**
Diabetes mellitus	1.08 (1.02-1.15)	**0.014**	NI	**-**	1.01 (0.96-1.06)	0.563
Dyslipidemia	0.80 (0.74-0.85)	**<0.001**	0.78 (0.73-0.84)	**<0.001**	0.79 (0.75-0.83)	**<0.001**
Heart failure	2.10 ((1.98-2.23)	**<0.001**	2.24 (2.10-2.40)	**<0.001**	1.32 (1.26-1.39)	**<0.001**
Chronic Kidney disease	1.30 (1.20-1.39)	**<0.001**	1.34 (1.25-1.44)	**<0.001**	1.32 (1.26-1.38)	**<0.001**
COPD	NI		1.14 (1.06-1.24)	**0.001**	1.13 (1.06-1.21)	**<0.001**
Ischemic heart disease	1.32 (1.20-1.45)	**<0.001**	1.17 (1.08-1.27)	**<0.001**	1.23 (1.15-1.31)	**<0.001**
Neoplasia	3.44 (3.16-3.74)	**<0.001**	3.47 (3.22.3.74)	**<0.001**	3.46 (3.27-3.67)	**<0.001**
Cirrhosis	2.49 (2.15-2.89)	**<0.001**	2.41 (2.16-2.69)	**<0.001**	2.43 (2.22-2.65)	**<0.001**
Neurodegenerative disease	1.50 (1.39-1.63)	**<0.001**	1.82 (1.642.02)	**<0.001**	1.61 (1.51-1.71)	**<0.001**
Hypothyroidism	0.81 (0.74-0.89)	**<0.001**	0.90 (0.77-1.06)	0.210	NI	
Lymphoma	2.03 (1.74-2.38)	**0.001**	2.00 (1.71-2.33)	**<0.001**	2.00 (1.79-2.24)	<0.001
Transplantation	NI		NI		NI	
HIV infection	1.52 (0.77-3.02)	0.226	1.25 (0.90-1.75)	0.173	1.30 (0.98-1.75)	0.083
Leukemia	4.45 (3.53-5.61)	**<0.001**	3.16 (2.54-3.93)	**<0.001**	2.19 (2.10-2.23)	**<0.001**
Clinical Complications						
Acute kidney failure	2.23 (2.16-2.45)	**<0.001**	2.08 (1.94-2.22)	**<0.001**	2.19 (2.10-2.30)	**<0.001**
Sepsis	3.58 (3.28-3.92)	**<0.001**	2.95 (2,62-3.26)	**<0.001**	3.29 (3.08-3.57)	**<0.001**
Severe sepsis	2.60 (2.30-2.92)	**<0.001**	2.41 (2.13-2.72)	**<0.001**	2.48 (2.28-2.78)	**<0.001**
ICU admission	1.89 (1.69-2.12)	**<0.001**	2.58 (2.34-2.84)	**<0.001**	2.23 (1.07-2.43)	**<0.001**

Abbreviations: COPD, chronic obstructive pulmonary disease; HIV: human immunodeficiency virus; ICD-10, International Classification of Diseases, 10th Revision; ICU, intensive care unit, NI, non-included in the multivariable analysis due to p value > 0.05 or nor clinically relevant; y, years.
In blond *P* value < 0.05.
[a] ICD-10 code.

Table 5
Economic burden of cellulitis hospitalization by sex and age group

	<65 y	65-79 y	> 80 y	Overall	Overall, mean
Hospitalization cost, total in million euros					
Women	116.9	137.8	197.0	451.8	64.4
Men	254.9	198.9	124.7	578.5	82.4
Overall, sum	371.9	336.6	321.7	1030.3	-
Overall, mean	53.14	47.9	45.7	146.8	-
Hospitalization cost, median (IQR) in euros					
Women	3560 (2548-4911)	3233 (3217-3223)	3698 (3223-5014)	3653 (3196-5017)	-
Men	3585 (2648-5098)	4178 (3233-6091)	3996 (3233-5242)	3669 (3196-5417)	-
Overall	3582 (2639-5075)	3996 (3233-5242)	3783 (3233-5092)	3653 (3196-5137)	-

Abbreviation: IQR, interquartile range; y, year.

study, among admitted patients, the mean of HRs were 63 and 76 per 100,000 person per years, respectively.

A review by Lagacé et al. [9] found that women with cellulitis were typically older and had more underlying conditions, such as chronic venous disease, while men were more likely to develop cellulitis from wounds. We observed a higher frequency of cellulitis in women aged 80 and above compared with men, consistent with previous studies [2,8,9,14]. However, the higher hospitalization rate for cellulitis in this age group may not necessarily indicate greater susceptibility among women. Instead, it could reflect the lower survival rate of men to this age due to other causes of mortality. This potential confounding factor should be considered when interpreting sex differences in hospitalization rates.

Lower-limb cellulitis was the most common localization in both sexes, consistent with other cohorts [9], with a slightly higher prevalence in women than in men. The trunk was the second most common location, with no significant differences between sexes. However, in Zalmanovic's cohort, trunk cellulitis was more frequent in women [17].

Our study highlighted that clinical and epidemiological differences associated with cellulitis in women included limb cellulitis, age groups 65-79 years and over 80 years, and comorbidities such as hypertension, dyslipidemia, obesity, heart failure, chronic peripheral vascular disease, and hypothyroidism. Conversely, characteristics less associated with cellulitis in women compared to men included cellulitis located on toes and hands, diabetes melli-

tus, smoking, COPD, chronic renal failure, ischemic heart disease, alcohol abuse, leukemia, neoplasm, cirrhosis, transplant, HIV infection, acute kidney failure, and ICU admission. Some differences may be explained by the varying prevalence of comorbidities between women and men.

Escherichia coli is the second most common pathogen in cellulitis cases, following *Staphylococcus* spp. However, *E. coli* is not typically a primary causative agent of cellulitis. This may be a confounding factor, partly due to the nature of administrative database used in our study. Additionally, we observed that infections in patients with cellulitis were more common among women (5.5% vs 3.7%). This may be attributed to a combination of anatomical, hormonal, and behavioral factors, as well as impaired immunity associated with conditions such as liver cirrhosis, chronic renal failure, postorgan transplantation, and hematologic malignancies. Immunosuppression results in a functional deficiency of polymorphonuclear cells, weakening the inflammatory response and increasing the susceptibility of immunocompromised patients to *E. coli* cellulitis through gastrointestinal or urinary translocation [18].

A study by Collazos et al. [8], conducted in Spain, identified cellulitis, age, edema, lymphedema, pus culture aggregation, and infection site (location on the trunk and head-neck) as significantly and independently associated with women. We agree with their findings regarding age and peripheral venous disease. However, pus data were not available in our administrative database. In contrast to their study, we found cellulitis was more commonly localized to the limbs rather than the trunk and face.

From an outcome perspective, mortality in our study was 7.4% in women and 5.9% in men, slightly higher than in other Spanish case series (3.1% and 2.9%, respectively) [8]. However, it was lower than the 14.9% mortality reported for patients with skin and soft tissue infections, which includes a broader range of conditions beyond cellulitis. Although Carratalá et al. [19] observed higher mortality in women, their study was based on a small number of events without multivariate analysis. Other studies have reported similar mortality rates between women and men [8,20]. In our study, while mortality was initially higher in women, this difference was not statistically significant after adjustment for other variables.

Regarding hospital stay, women had slightly shorter hospitalizations in our study. This aligns with findings from other small studies [21,22].

We separately analyzed mortality risk factors for women and men. In women, increased mortality was associated with cellulitis of the trunk, age ≥80 years, leukemia, neoplasia, lymphoma, cirrhosis, heart failure, neurodegenerative diseases, ischemic heart disease, chronic renal failure, and diabetes mellitus. Consistent with other studies, chronic renal disease and heart failure were also significant predictors of mortality [23]. Cancer patients, who are more susceptible to infections, showed a more than twofold increased risk of death [24]. Complications such as sepsis, severe sepsis, acute kidney failure, and ICU admission were also associated with higher mortality, consistent with previous research [20].

Economic data on cellulitis-related hospitalizations are limited. In Wales, the direct annual cost for managing cellulitis was estimated at £28 million, including £19.6 million for admitted patients [25]. In our study, the mean annual cost for hospitalizations was €64.4 million for women and €82.4 million for men, totaling €146.8 million. While the median cost for admitted patients in the USA was $6,400 in 2014 [26], our study reported a lower median cost of €3,653, with minimal differences between sexes. However, international comparisons should account for differences in healthcare systems and cost imputations.

The strength of this study lies in its sex-focused approach, utilizing an administrative database to provide insights into the number of annual cases, HR, clinical characteristics, economic factors, and mortality risk factors for cellulitis.

However, it is important to acknowledge certain limitations associated with the use of administrative databases [27]. First, hospital discharge records document hospital admissions, with each admission—including readmissions—counted as a new episode. Consequently, some patients may have been included more than once. Second, the information available for each patient is restricted to the set of diagnoses coded at hospital discharge. In some cases, only the diagnoses considered most relevant by the attending clinician are recorded. Diagnostic coding can be particularly challenging for conditions lacking specific tests or well-defined pathologies for confirmation. The variability in how clinicians document diagnostic codes introduces inconsistencies and potential inaccuracies in the data. This lack of specificity can result in both overdiagnosis and underdiagnosis of medical conditions. Third, the coded diagnosis of infection by a microorganism is assumed to indicate that the microorganism was identified in a culture isolate (either from blood or another site). However, it is possible that the patient had an *E. coli* infection from another source in addition to cellulitis. This highlights a limitation of administrative databases, as they may not be the most reliable tools for evaluating the specific pathogens responsible for infections. Finally In administrative databases, sepsis is identified using two codes: A40.x (streptococcal sepsis) and A41.x (other sepsis) and severe sepsis is coded as ICD-10: R65.2. This may have influenced the study results, as the ORs for sepsis is higher than that for severe sepsis. This finding is counterintuitive, as severe sepsis generally represents a more critical condition with a higher mortality risk.

In conclusion, our findings indicate a stable hospitalization rate during the study period, except for a decrease during the COVID-19 pandemic. Women with cellulitis tended to be older and had fewer admissions, except in those over 80 years. No significant differences in mortality were observed between sexes after adjusting for other variables. Mortality was associated with factors such as age ≥80 years, trunk cellulitis, comorbidities, and severe complications, including sepsis and renal failure. The average cost of admission was slightly lower for women than for men. These findings underscore the importance of using administrative databases to explore sex-based differences in cellulitis and other infectious diseases.

Authors' contributions

Study design: I. Belinchón-Romero, E. Merino and J.M. Ramos-Rincón and Data collection: I. Belinchón-Romero, and J.M. Ramos-Rincón. Data analysis: J.M. Ramos-Rincón. Writing: Belinchón-Romero, E. Merino, I and J.M. Ramos-Rincón.

Ethical approval statement

The research protocol was approved by the Committee of Ethics and Integrity in Research of Miguel Hernández University (ref. AUT.DMC.JMRR.241103).

Availability of data and materials

According to the contract signed with the Spanish Ministry of Health, which provided access to the databases from the Spanish National Hospital Database, we cannot share the databases with any other investigator. Consequently, we cannot upload the databases to any public repository. The data that support the findings of this study are available from the corresponding author upon reasonable request

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

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