Clinical Features and Predictors for Mortality in Neurolisteriosis: An Administrative Data-Based Study

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Abstract: Listeriosis is an uncommon and potentially severe zoonotic bacterial infection that usually occurs in outbreaks instead of isolated cases. In recent years, there has been an increase in the incidence of this disease. One of the most severe of its complications involves the central nervous system (CNS) in a condition known as neurolisteriosis. Here, we describe the demographic and clinical features of patients presenting with neurolisteriosis between 2001 and 2015 using administrative data and attempt to identify potential predictors for mortality. We used the Spanish Minimum Basic Data Set at Hospitalization, a compulsory registry that collects data from clinical discharge reports. Up to 2015, data were coded based on the International Classification of Diseases, 9th Revision, so we used diagnoses and clinical conditions based on these codes. Age, sex, clinical presentation, mortality, and involvement of the CNS were identified. Using algorithms to aggregate data, variables such as immunosuppression and malignant disease were obtained. We analyzed correlations among clinical features and identified risk factors for morbidity and mortality. Between 2001 and 2015 we identified 5180 individuals, with a hospitalization rate of 0.76 per 100,000 population. Most (94%) were adults, and only 5.4% were pregnant women. The average age was 66 years. Neurological involvement was present in 2313 patients (44.7%), mostly meningitis (90.4%). Global mortality was 17%, but mortality in CNS infections was 19.2%. Age, severe sepsis, chronic liver disease, chronic kidney disease, and malignancy were the main risk factors for mortality in patients with CNS infections by Listeria monocytogenes. Although it is uncommon, neurolisteriosis can be a severe condition, associated with a high rate of mortality. Health care providers should be aware of potential sources of infection so that appropriate measures can be taken to prevent it.

Keywords: Listeria monocytogenes; neurolisteriosis; meningitis; mortality; risk factors

1. Introduction

Listeriosis is an infection caused by Listeria monocytogenes, a Gram-positive bacterium that can cause a wide spectrum of clinical presentations in humans, from neonatal infection to neuroinvasive disease. Listeriosis is infrequent in humans, because L. monocytogenes is more commonly seen in ruminants [1]. Listeria usually spreads through contaminated food [2]. Regarding humans, in severe syndromes the main risk factors are immunosuppression, the presence of solid or hematological malignancy, extreme age (being either elderly or a newborn), and pregnancy [3,4]. Therefore, recent studies [4,5] highlighted the role of malignancies, and immunosuppression as the most frequently recorded comorbid conditions in non-pregnant patients, which had a great impact on mortality and clinical sequelae. The MONALISA study found that central nervous system (CNS) infections, along with immunosuppression and malignancy had three-fold higher mortality [4]. Other studies found that patients with no underlying conditions usually have a good prognosis [6–8]. Although the prognosis in pregnant women is usually good, listeriosis during pregnancy can cause abortion, premature delivery, fetal mortality, and severe neonatal morbidity [9,10]. Listeriosis is usually diagnosed by positively isolating the pathogen in
blood culture. In neuroinvasive infection, cultures of cerebrospinal fluid are positive, but blood cultures are often negative [3,11].

Regarding CNS infections, bacterial meningitis is a severe syndrome with quick symptom onset. Its incidence is estimated to be 4 to 6 adults per 100,000 population/year in developed countries, but it may be higher in developing countries [12]. *Streptococcus pneumoniae* and *Neisseria meningitidis* are the main pathogens in bacterial meningitis in adults, causing up to 85% of all cases [13], and *Listeria monocytogenes* is the third most frequently encountered cause [14,15]. Again, older age and immunosuppression are the main predictors of mortality in *Listeria*-related meningitis [4,16]. Not only meningitis, but meningoencephalitis and brain abscess are severe forms of neuroinvasive listeriosis and risk factors for morbidity and mortality, and several studies have emphasized the importance of neurological syndromes for the severity of listeriosis. Arslan et al. [11] found that CNS infections were an independent risk factor for mortality, and parenchymal involvement in neuroimaging was an independent risk factor for severe infection. Brouwer et al. [15] found a mortality rate of 17%, with immunocompromised status as the main risk factor for mortality in neurological involvement. Goulet et al. [16] reported that more than 50% of their patients developed severe sepsis, with 20–25% having neurological infections.

In this study, we described the demographic and clinical features related to the neurological involvement of infections by *L. monocytogenes*. Using administrative data, we determined the risk factors in morbidity and mortality related to infections of the CNS. Performing such analyses may shed light on the relevance of neurological features to the broad spectrum of symptoms showed by listeriosis.

2. Materials and Methods

2.1. Study Population

We used administrative data collected from the Statistical Site of the National Health System, which supplies information and statistics on health and health services in Spain aimed at managerial, care, and academic professionals. Data were collected using the Minimum Basic Data Set (MBDS) between 2001 and 2015. The MBDS is a mandatory registry that covers 99.5% of the population of Spain [17]. A total of 14 variables are recorded from patients’ hospitalization reports at discharge. For our study, we chose collected data up to 2015, because records were encoded using the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). Listeriosis was encoded as 027.0 either in the Main Diagnosis or Secondary Diagnosis fields. Age, sex, main and secondary diagnoses, date of admission, and date of discharge were collected. Other demographic variables, such as insurance, billing data, and hospital features, were excluded. The variables collected from the MBDS are listed in Table 1. Critical data that may potentially identify patients are encoded using a hash function, so a hash value is returned instead of the critical value (patient or hospital identifier).

| Feature Name                                      | Type       |
|--------------------------------------------------|------------|
| Patient’s hospital medical record number (hash)  | numeric    |
| Patient identifier (hash)                        | numeric    |
| Department                                       | categorical|
| Date of birth                                    | date       |
| Date of admission                                | date       |
| Date of discharge                                | date       |
| Type of discharge                                | categorical|
Table 1. Cont.

| Feature Name                                         | Type       |
|------------------------------------------------------|------------|
| Main diagnosis + 14 secondary diagnoses (if applicable)| categorical|
| Main procedure + 20 secondary procedures (if applicable) | categorical|
| Type of admission (urgent/scheduled)                  | categorical|
| Hospital (hash)                                      | numeric    |
| Postal code                                          | categorical|
| Billing/insurance type                                | categorical|
| Date of surgical intervention                         | date       |

2.2. Feature Engineering and Preprocessing

Dealing with administrative data may be challenging. First, clinical data regarding medical conditions are encoded according to a standard system of assigning codes to diagnoses and procedures, but critical data such as clinical presentation are missing. Therefore, some conditions must be created from scratch. For instance, there is no code for “immunosuppression” because it is a clinical condition, not a diagnosis, so feature engineering must be used to combine certain encoded diagnoses to build this clinical condition from scratch. In addition, some demographic and insurance data were omitted, as these data would likely only have added noise to the final data set.

On the basis of 027.0 as the code for “listeriosis”, we identified patients with meningitis or meningencephalitis (code 320.7), encephalomyelitis (code 323.0), intracranial abscess (code 324.0), bacterial endocarditis (code 421), febrile gastroenteritis (codes 008, 009, and 558), and sepsis and septic shock (codes 995 and 785). Other medical conditions analyzed as predictors were also collected: type 1 and type 2 diabetes mellitus, solid and hematological malignancies, immunosuppression, chronic kidney disease (CKD), chronic liver disease, and chronic obstructive pulmonary disease (COPD) [18].

2.3. Analyses of Features

All analyses were performed in R, version 3.6.1 (Vienna, Austria, 5 July 2019) [19]. Data are reported as absolute values and percentages or medians and interquartile ranges (IQRs), as appropriate. To perform bivariate (correlational) analyses, we used the chi-square test for categorical variables and the Mann–Whitney–Wilcoxon U test for continuous variables. For multivariate analyses, we used logistic regression, with mortality as a binary variable (yes/no); odds ratios (ORs) were calculated. We used a p-value of 0.05 as the threshold for statistical significance.

3. Results

3.1. Descriptive Analyses

Table 2 summarizes the main features of the studied population. Data from 5180 hospitalized patients were collected between 2001 and 2015. The average rate of annual hospitalization was 0.76 per 100,000 population, ranging from 0.48 in 2001 to 0.96 in 2015 (Figure 1). The trend was therefore upward, with a maximum rate of 1.01 hospitalized patients per 100,000 inhabitants in 2015 [20]. Women made up 41.1% of the patients, and there were 291 (5.6%) cases of newborns. Therefore, 94.4% of the total sample were young and adult patients. Of those, only 5.4% were pregnant women. If newborns are excluded, the median age was 66 (IQR 18.2), as seen in Figure 2.
The most frequent clinical presentation was neurolisteriosis, in any neurological manifestation, with 2313 patients (44.7%). Sepsis and septic shock (9%), febrile gastroenteritis (4.1%), and endocarditis (0.9%) were uncommon among hospitalized patients with listeriosis. Immunosuppression (42.9%), malignancy (25.9%), and chronic liver disease (13.7%) were the most recorded comorbidities in discharge reports. During their hospital stay, 879 individuals (17%) died. The most common causes of death were neurolisteriosis (443 patients, 50%) and sepsis (190 patients, 21%).

As noted, 2313 individuals were diagnosed with one of the three neurological conditions considered in this study. The most frequent diagnosis was meningitis (90.4%), while encephalomyelitis (6.7%) and intracranial abscess (4.9%) accounted for the remaining cases of neurolisteriosis. In the group with CNS involvement, there were more men than women (64.8% versus 35.2%). Median age was 64. Only 1 pregnant woman was diagnosed with neurolisteriosis, and 280 did not present with neurological involvement.
Table 2. Demographic and clinical features of the general study population and the subset with neurological involvement.

|                          | Total (n = 5180) | Neurolisteriosis (n = 2313) |
|--------------------------|------------------|----------------------------|
| Sex (women)              | 2130 (41.1%)     | 815 (35.2%)                |
| Newborns                 | 291 (5.6%)       | 112 (4.8%)                 |
| Pregnancy                | 281 (5.4%)       | 1 (0.001%)                 |
| Adults                   | 4889 (94.4%)     | 2.201 (95%)                |
| Age, all patients (median)| 65 (22.6)        | 64 (21.2)                  |
| Age, only adults (median) | 66 (18.2)        | 65 (22.6)                  |

Clinical presentation

|                          | Total (n = 5180) | Neurolisteriosis (n = 2313) |
|--------------------------|------------------|----------------------------|
| Neurological (all)       | 2313 (44.7%)     | 2313 (100%)                |
| Meningitis               | 2090 (40.3%)     | 2090 (90.4%)               |
| Encephalomyelitis        | 156 (3.0%)       | 156 (6.7%)                 |
| Intracranial abscess     | 113 (2.2%)       | 113 (4.9%)                 |
| Endocarditis             | 45 (0.9%)        | 8 (0.3%)                   |
| Febrile gastroenteritis  | 212 (4.1%)       | 51 (2.2%)                  |
| Sepsis/septic shock      | 465 (9.0%)       | 167 (7.2%)                 |
| Death                    | 879 (17.0%)      | 443 (19.2%)                |

Comorbidities

|                          | Total (n = 5180) | Neurolisteriosis (n = 2313) |
|--------------------------|------------------|----------------------------|
| Diabetes mellitus        | 822 (15.9%)      | 340 (14.7%)                |
| COPD                     | 492 (9.5%)       | 219 (9.5%)                 |
| Chronic liver disease    | 710 (13.7%)      | 247 (10.7%)                |
| Chronic kidney disease   | 468 (9.0%)       | 124 (5.4%)                 |
| Immunosuppression        | 2.222 (42.9%)    | 810 (35%)                  |
| Malignancy               | 1341 (25.9%)     | 412 (17.8%)                |

Age is reported as median and interquartile range, whereas the remaining variables are reported as absolute values and percentages. COPD: Chronic obstructive pulmonary disease.

3.2. Bivariate and Multivariate Analyses

The second objective of our research was to identify features associated with mortality among patients presenting with neurolisteriosis. Table 3 shows the results of bivariate analyses used to find correlations between variables of interest and mortality. Age, sepsis/septic shock, chronic liver disease, CKD, immunosuppression, and malignancy (either solid or hematological) showed a positive association with the probability of death in patients presenting with CNS involvement. With the relevant variables yielded in bivariate analyses, we performed a logistic regression, and ORs were calculated. Age, sepsis and septic shock, chronic liver disease, CKD, and malignancy, but not immunosuppression, were confirmed as predictors for mortality (Table 4).

Table 3. Mortality in patients diagnosed with any form of neurolisteriosis, including listeriosis-related diagnoses and comorbidities, assessed via bivariate analyses.

|                          | Mortality (n = 443) | Survival (n = 1870) | p-Value |
|--------------------------|---------------------|---------------------|---------|
| Sex (women)              | 168 (37.9%)         | 647 (34.6%)         | 0.207   |
| Newborns                 | 5 (1.1%)            | 107 (5.7%)          | <0.001  |
| Pregnancy                | 0 (0.0%)            | 1 (0.1%)            | 0.999   |
| Age, in years (median, IQR) | 73 (15.9)        | 62 (21.6)           | <0.001  |
| CNS involvement          |                      |                     |         |
| Meningitis               | 403 (91%)           | 1687 (90.2%)        | 0.692   |
| Encephalomyelitis        | 33 (7.4%)           | 123 (6.6%)          | 0.580   |
| Intracranial abscess     | 23 (5.2%)           | 90 (4.8%)           | 0.833   |
| Other manifestations     |                      |                     |         |
| Endocarditis             | 2 (0.5%)            | 6 (0.3%)            | 0.999   |
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Table 3. Cont.

| Condition                        | Mortality (n = 443) | Survival (n = 1870) | p-Value |
|----------------------------------|---------------------|---------------------|---------|
| Febrile gastroenteritis          | 5 (1.1%)            | 46 (2.5%)           | 0.124   |
| Sepsis/septic shock              | 78 (17.6%)          | 89 (4.8%)           | <0.001  |
| Comorbidities                    |                     |                     |         |
| Diabetes mellitus                | 74 (16.7%)          | 266 (14.2%)         | 0.211   |
| COPD                             | 46 (10.4%)          | 173 (9.3%)          | 0.521   |
| Chronic liver disease            | 62 (14%)            | 185 (9.9%)          | 0.150   |
| Chronic kidney disease (CKD)     | 45 (10.2%)          | 79 (4.2%)           | <0.001  |
| Immunosuppression                | 195 (44%)           | 615 (32.9%)         | <0.001  |
| Malignancy                       | 130 (29.3%)         | 282 (15.1%)         | <0.001  |

COPD: Chronic obstructive pulmonary disease. CKD: Chronic kidney disease. CNS: Central nervous system.

Table 4. Results of multivariate analyses using logistic regression in our population with neurolisteriosis.

| Risk Factor                      | Odds Ratio | 2.5% | 97.5% | p-Value |
|----------------------------------|------------|------|-------|---------|
| Age                              | 1.039      | 1.031| 1.047 | <0.001  |
| Sepsis/septic shock              | 4.527      | 3.190| 6.430 | <0.001  |
| Chronic liver disease            | 1.625      | 1.161| 2.250 | 0.004   |
| Chronic kidney disease (CKD)     | 2.048      | 1.355| 3.061 | <0.001  |
| Immunosuppression                | 1.133      | 0.838| 1.521 | 0.410   |
| Malignancy                       | 2.154      | 1.540| 3.025 | <0.001  |

CKD: Chronic kidney disease.

4. Discussion

Our main aim in this study was to describe the demographic and clinical features of patients diagnosed with listeriosis from administrative data sources. The incidence in Spain between 2001 and 2015 was 0.76 per 100,000 population, higher than 0.47, the overall value for the European Union (EU) in the same period [21]. Indeed, a recent study [5] reported an increase in global incidence from 2008, probably related to aging, increased life expectancy particularly among immunocompromised patients [21], and changes in food safety measures, food consumption patterns, and food industry processes [22]. Some studies have found associations between foodborne diseases and undercooked beef, chicken, and eggs [23].

The higher incidence in Spain than in other countries in the EU indicates a need to focus on prevention and control of this foodborne disease [5]. MBDS data suggest that the incidence of this disease is increasing, and it will probably continue to increase in the immediate future. Furthermore, given that notification of listeriosis has been compulsory since 2015 [24], an increased global incidence of listeriosis and of CNS involvement are expected, with subsequent increased mortality.

Our study demonstrates that neurolisteriosis is the most frequent clinical presentation in hospitalized patients (44.7%). However, it is worth noting that not all clinical forms of listeriosis require hospitalization. For instance, mild gastroenteritis does not require a hospital stay, and therefore, this condition is not recorded in hospitalization records in such cases. This may be a limitation to our research. Mortality due to listeriosis was 17% in our study and was related to aging, in line with other European epidemiological studies, in which mortality was 16.6% [21]. If involvement of the CNS is present, mortality can reach 30%, even with appropriate treatment [4,25]. According to our own data, mortality due to neurolisteriosis was 19%, lower than the average in the EU but a high rate, nevertheless.

*Listeria monocytogenes* is less likely to cause neurological involvement than other pathogens. *Streptococcus pneumoniae* and *Neisseria meningitidis* are the main causes of meningitis in adults [13]. However, clinical presentation and mortality are more severe in cases of neurolisteriosis. We found that meningitis was the most common CNS presentation (91%), and far behind, encephalomyelitis and intracranial abscesses, as has been found in earlier studies of neuroinvasive listeriosis [11]. Severity was associated with age and other predisposing factors, such as malignancy (either solid tumor or hematological condition), chronic disease (either
renal or hepatic), and concurrent presence of sepsis. Some authors have reported diabetes mellitus and immunosuppression as risk factors for mortality [15,26], but that was not the case in our study. Our hypothesis for explaining these differences in risk factors relates to the inherent limitations of performing this study with administrative data collected from discharge reports. This can lead to the loss of certain clinical conditions that could not be encoded in the MBDS system, as is discussed below.

Limitations

Even with the advantage that our database was constructed from data on about 99% of the Spanish hospitalized population, the data were collected from diagnoses reported at discharge. Asymptomatic patients or patients who did not require hospitalization were not recorded, and the real incidence was therefore underestimated. In addition, our database did not include symptoms, main complaints, or clinical or laboratory features. MBDS does not include antibiotic treatment or an indication of whether antibiotic therapy was delayed, as has been discussed in other studies [4,5,11,27]. Another major limitation is that we did not access data on neurological sequelae of neurolisteriosis. Additionally, as mentioned in the Methods section, feature engineering was required to build from scratch the variable “immunosuppression”, which probably underestimated the real immunosuppression data because the registry is limited in terms of immunosuppressive agents and cytotoxic therapies. We built this variable from a combination of conditions proposed by Greenberg et al. [28] and using the ICD-9. In the cited study, to define immunosuppression, the authors included HIV, malignancies, certain blood dyscrasias such as agranulocytosis, organ transplantation, and certain chronic inflammatory diseases that usually require immunosuppressive drugs. From a purely statistical point of view, malignancy and immunosuppression were correlated variables, but logistic regression could handle multicollinearity in such a way that immunosuppression was dropped as a potential predictor. Finally, we included data up to 2015, when the ICD-9 was still used to encode data. Since then, the ICD-10 has been used, and the gap in data up to the present can be an interesting line of future research.

5. Conclusions

Neurolisteriosis, according to published series in the medical literature, is the third- or fourth-ranked cause of meningitis, but the resulting condition can be more severe than is seen in the usual pathogens, as the mortality rate is high (up to 19% of hospitalized patients). Most cases of systemic listeriosis that require hospitalization are caused by neurolisteriosis (44% of cases). Mortality due to neurolisteriosis in Spain is lower than in the EU, but it remains at a high level. Aging, sepsis, malignancies, and chronic disease are the most important predictors of mortality in these patients. The increase in listeriosis observed over the past decade indicates that providers and state governments should move to combine preventive actions with improved sanitary procedures regarding food safety, particularly for at-risk populations.

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Institutional Review Board Statement: All procedures involving human participants were conducted in accordance with the ethical standards of the responsible institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. This study was approved by the Ethical Board of Mostoles University Hospital.

Informed Consent Statement: Not applicable.

Data Availability Statement: According to a contract signed with Mostoles University Hospital and the Spanish Ministry of Health, which provided the database, we cannot provide our database to any other researcher. Furthermore, we must destroy the database once our investigation has concluded. The data cannot be uploaded to any public repository. However, the data can be obtained from the Spanish Ministry of Health at Portal Estadístico: https://pestadistico.inteligenciadegestion.mscbs.es/publicoSNS/Comun/DefaultPublico.aspx (accessed on 22 December 2017).
Conflicts of Interest: The author declares no conflict of interest.

Abbreviations

The following abbreviations are used in this manuscript:

ICD-9 International Classification of Diseases, 9th Revision
ICD-10 International Classification of Diseases, 10th Revision
MBDS Minimum Basic Data Set
COPD Chronic obstructive pulmonary disease
CKD Chronic kidney disease
OR Odds ratio
CNS Central nervous system
EU European Union

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