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ORIGINAL RESEARCH

Clinical Characteristics and Fatality Risk Factors for Patients with *Listeria monocytogenes* Infection: A 12-Year Hospital-Based Study in Xi'an, China

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ABSTRACT

Introduction: Listeriosis is a severe food-borne disease caused by *Listeria monocytogenes* infection. The data of listeriosis in Xi'an population are limited. The aim of this study is to evaluate the clinical features and fatality risk factors for listeriosis in three tertiary-care hospitals in Xi'an, China

Methods: The characteristics of demographic data, underlying diseases, clinical manifestations, laboratory indicators, cranial imaging examination, antibiotics therapeutic schemes, and clinical outcomes were collected between 2011 and 2023. Logistic regression analysis was performed.

Results: Seventy-one etiologically confirmed listeriosis patients were enrolled, including 12 neonatal and 59 non-neonatal cases. The majority of neonatal listeriosis presented as preterm (50%) and fetal distress (75%). The main clinical manifestations of non-neonatal listeriosis included fever (88%), headache (32%), disorder of consciousness (25%), vomiting (17%), abdominal pain (12%), and convulsions (8%). The fatality rate in neonatal cases was higher than in non-neonatal listeriosis (42 vs. 17%). Although no deaths were reported in maternal

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listeriosis, only two of 23 patients had an uneventful obstetrical outcome. Five maternal listeriosis delivered culture-positive neonates, three of whom decreased within 1 week postgestation due to severe complications. Twenty-eight cases were neurolisteriosis and 43 cases were bacteremia. Neurolisteriosis had a higher fatality rate compared with bacteremia listeriosis (36 vs. 12%). The main neuroradiological images were cerebral edema/hydrocephalus, intracranial infection, and cerebral hernia. *Listeria monocytogenes* showed extremely low resistance to ampicillin (two isolates) and penicillin (one isolate). The fatality risk factors were the involvement of the central nervous system, hyperbilirubinemia, and hyponatremia for all enrolled subjects. Hyperuricemia contributed to the elevation of fatality risk in non-neonatal listeriosis.

Conclusions: When the patients suffered with symptoms of fever and central nervous system infection, they should be alert to the possibility of listeriosis. Early administration of ampicillin- or penicillin-based therapy might be beneficial for recovery of listeriosis.

Keywords: *Listeria monocytogenes*; Bacteremia; Neurolisteriosis; Prognosis; Risk factor

Key Summary Points

Why carry out this study?

Listeriosis, which is caused by *Listeria monocytogenes* infection, presents a variety of syndromes, ranging from subclinical and uncomplicated febrile gastroenteritis to severe invasive infection. The data of listeriosis in Xi'an population are limited.

We want to analyze the clinical characteristics, outcomes, and risk fatality factors of listeriosis from three tertiary-care hospitals in Xi'an between 2011 and 2023.

What was learned from the study?

The main presentations of neonatal listeriosis were preterm and fetal distress, with higher fatality rate. The main clinical manifestations of non-neonatal listeriosis were fever, headache, disorder of consciousness, vomiting, abdominal pain, and convulsions. Maternal listeriosis always led to eventful obstetrical outcomes.

The fatality risk factors were the involvement of the central nervous system, hyperbilirubinemia, and hyponatremia for all enrolled subjects. Hyperuricemia contributed to the elevation of fatality risk in non-neonatal listeriosis.

When patients suffer from symptoms of fever and central nervous system infection, they should be alert to the possibility of listeriosis. Early administration of ampicillin- or penicillin-based therapy might be beneficial for recovery of listeriosis.

INTRODUCTION

Listeria monocytogenes (*L. monocytogenes*) is a Gram-positive intracellular pathogen that is widespread in the environment [1]. The main routes of *L. monocytogenes* transmission are believed to be contracted through consumption of contaminated food (especially processed meat, prepared vegetables and fruits, pre-packed sandwiches, soft cheeses, and unpasteurized milk) [2–6] and vertical transmission from mother to newborn [7–9]. *L. monocytogenes* infection in human, which is known as listeriosis, is mostly sporadic, but food-borne outbreaks are also observed [10–12]. Listeriosis presents a variety of syndromes in humans, ranging from subclinical and uncomplicated febrile gastroenteritis to severe invasive infection [1, 13]. Invasive listeriosis can be categorized into three main clinical forms, including non-maternal listeriosis, maternal listeriosis, and neonatal listeriosis. Non-maternal listeriosis also mainly manifests as bacteremia or septicemic listeriosis as well as central nervous system infection, such as meningitis or meningoencephalitis (generically

referred as neurolisteriosis) [1, 13, 14]. Listeriosis manifestations also include peritoneal cavity infection, osteoarthritis, pneumonia, myocarditis, urinary tract infection, and endophthalmitis, accounting for approximate 1% of total *L. monocytogenes* infections [1].

The estimated incidence of listeriosis ranges between 0.1 and 11.3 cases per 100,000 persons, depending on geographical location and surveillance [5]. Most listeriosis cases have been reported from industrialized Western countries. In the United States, the Foodborne Disease Active Surveillance Network has been implementing laboratory-based surveillance in listeriosis epidemiology since 1996 [1], revealing a stable incidence rate estimated to be 0.3 per million population in United States over the period from 2006 to 2022 [15–17], leading *L. monocytogenes* as the fourth causative pathogen in bacterial meningitis [18]. Since 2000, China has made strong effects and improved surveillance systems for monitoring and controlling listeriosis [14, 19]. Feng et al. reviewed the listeriosis patients reported in China from 1964 to 2010 and found 147 sporadic listeriosis cases reported, with the only outbreak recorded among students in an elementary school in Zhejiang Province in October of 2003 [20]. Chen et al. also investigated listeriosis in China from 2008 to 2017 and showed that 759 cases were reported from 22 provinces, with an overall fatality rate of 18% [19]. All listeriosis cases were recorded as being sporadic, and no outbreaks were reported during this period [19, 21]. However, the data is still limited regarding the clinical features and prognostic factors of *L. monocytogenes* infection in China due to the relatively late start of the monitoring system [14, 19]. In particular, there were limited investigations describing *L. monocytogenes* infection in Xi'an, China. Thus, we retrospectively reviewed all identified listeriosis cases in three tertiary-care hospitals in Xi'an, Shaanxi Province, from 2011 to 2023, and described the clinical characteristics, outcomes, and risk factors of death of *L. monocytogenes*-infected patients.

METHODS

Ethics

The study protocol was approved by the Institutional Review Board of Tangdu Hospital (No. K202309-10), Shaanxi Provincial People's Hospital (No. 2023-0135), and The Second Affiliated Hospital of Xi'an Medical University (No. 23EC027). This study involving human participants was in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. We used an anonymized database for all analyses, and all potentially identifying variables were removed.

Definition and Data Collection

This was a hospital-based retrospective study on patients infected with *L. monocytogenes* from May 2011 to July 2023 in the above three tertiary care hospitals in Xi'an. The diagnosis of listeriosis was based on one of the following factors: isolation of *L. monocytogenes* from blood, cerebrospinal fluid (CSF), or placenta; detection of *L. monocytogenes* species-specific reads in body fluid using metagenomic next-generation sequencing (mNGS). The cases were categorized as maternal, neonatal, and non-maternal infections [22]. Maternal infection was defined based on the isolation of *L. monocytogenes* from pregnant women [13, 14, 22]. Neonatal infection was defined based on the isolation of *L. monocytogenes* from 1-month-old or younger neonates [14, 22]. Bacteremia was defined as isolation or detection of *L. monocytogenes* from blood without neurolisteriosis [13, 14]. Neurolisteriosis was defined as isolation or detection of *L. monocytogenes* from CSF or isolation of *L. monocytogenes* from blood while accompanied by symptoms of central nervous system infection [13, 14].

Clinical data from identified cases were abstracted from the medical records, including demographic information, underlying diseases, sites from which the organism was isolated or detected, clinical manifestations, laboratory

indicators when identified as listeriosis, cranial imaging examinations, anti-microbial therapeutic schemes, and clinical outcomes.

Statistical Analyses

Statistical analyses were performed using SAS Version 9.4 (SAS Institute Inc, Cary, NC, USA) and SPSS Version 25.0 (IBM SPSS Software, Chicago, IL, USA). For categorical variables, data were presented as *n* (%). Fisher's exact test was used for comparison. Continuous variables following normal distribution were presented as mean ± standard deviation. Student's *t* test was used for comparison between two groups. One-way analysis of variance was used for comparison among groups, and Student–Newman–Keuls-*q* test was further used for comparison between the two groups. Continuous variables following skewed distribution were presented as median (interquartile range) [M (Q1, Q3)]. Mann–Whitney *U* test was used for comparison between two groups. Kruskal–Wallis *H* test was used for comparison among groups, and Dunn's multiple comparison test was further used for comparison between the two groups. The influencing factors of death were examined using univariate and multivariate stepwise logistic regression models, with results expressed as odds ratios (OR) with 95% confidence intervals (CI). A *P* value less than 0.05 was considered statistically significant.

RESULTS

Characteristics of Neonatal and Non-neonatal Listeriosis

A total of 71 patients with listeriosis, including 12 neonatal and 59 non-neonatal cases, diagnosed between 2011 and 2023 in three tertiary hospitals in Xi'an, Shaanxi Province, China. The clinical characteristics of neonatal and non-neonatal listeriosis are shown in Table 1. All neonatal listeriosis were diagnosed less than 6 days of life (age range, 20 min ~ 4 days) and were identified as early onset infection. The majority of neonatal cases presented as preterm (50%) and fetal distress (75%). The fatality rate in the neonatal group was slightly higher than in the non-neonatal group (Table 1; 42 vs. 17%). The main clinical manifestations in non-neonatal group included fever (88%), headache (32%), disorder of consciousness (25%), vomiting (17%), abdominal pain (12%), and convulsions (8%). Twenty-three non-neonatal listeriosis patients had underlying diseases (Table 1). Among them, seven cases were receiving steroid administration and nine cases were receiving chemotherapy. Both groups had elevated median white blood cell (WBC) count ($>10\times10^9$/l). The mean percentage of neutrophils was elevated in the non-neonatal group but was in the normal range in the neonatal group (Table 1). The median aspartate aminotransferase (AST) and total bilirubin (T-BIL) levels were elevated, while the median albumin and globulin levels were reduced in the neonatal group (Table 1). The median procalcitonin level was also strongly increased in the neonatal group (Table 1).

Characteristics of Maternal Listeriosis and the Connection with Neonatal *L. monocytogenes* Infection

There were 23 maternal cases of listeriosis identified. Thirteen patients were confirmed by isolation of *L. monocytogenes* from blood, while ten patients were diagnosed by isolation of *L. monocytogenes* from placenta. The mean gestation was 26.61 ± 6.79 weeks (range, 14 ~ 38 weeks). Twelve maternal infections (52%) occurred in the second trimester of pregnancy (14 ~ 28 weeks), and 11 patients (48%) were recognized in the third trimester of pregnancy (> 28 weeks). The median WBC count [16.76 (14.13, 21.08) $\times 10^9$/l] and CRP level [88.00 (52.84, 116.2) mg/l] was strongly elevated. None of the maternal infections had central nervous system involvement and all cases fully recovered after delivery. Two cases had normal pregnancy outcome, and one case had paraplegia in a newborn (hedratresia). There were 15 abortions as a result of *L. monocytogenes* infections (11 cases in the second trimester and four cases in the third trimester of pregnancy). Importantly, obstetrical outcomes included five cases of listeriosis in the infants

Table 1 Clinical characteristics of neonatal and non-neonatal listeriosis

	Neonatal listeriosis	Non-neonatal listeriosis
Case (*n*)	12	59
Age (years) (range)	20 min ~ 4 days	41.88 ± 16.99 (2 ~ 78)
Male gender (*n*, %)	5 (42%)	23 (39%)
Female gender (*n*, %)	7 (58%)	36 (61%)
Bacteremia (*n*, %)	8 (67%)	35 (59%)
Neurolisteriosis (*n*, %)	4 (33%)	24 (41%)
Survive (*n*, %)	7 (58%)	49 (83%)
Death (*n*, %)	5 (42%)	10 (17%)
Underlying disease	Not available	23 (39%)
Hematological disease	Not available	7 (12%)
Hypertension	Not available	6 (10%)
Autoimmune disease	Not available	6 (10%)
Diabetes	Not available	3 (5%)
Neoplasm	Not available	2 (4%)
Liver cirrhosis	Not available	2 (4%)
AIDS	Not available	1 (2%)
Nephrotic syndrome	Not available	1 (2%)
Bipolar disorder	Not available	1 (2%)
Clinical manifestation		
Fever	2 (17%)	52 (88%)
Headache	0 (0%)	19 (32%)
Disorder of consciousness	0 (0%)	15 (25%)
Vomiting	0 (0%)	10 (17%)
Abdominal pain	0 (0%)	7 (12%)
Convulsion	0 (0%)	5 (8%)
Preterm	6 (50%)	Not available
Fetal distress	9 (75%)	Not available
Blood routine test		
WBC ($\times 10^9$/l)	10.61 (4.91, 15.55)	12.10 (6.97, 19.09)
Neutrophils (%)	63.22 ± 20.05	80.27 ± 11.70
Lymphocytes ($\times 10^9$/l)	1.79 (0.92, 2.54)	1.26 (0.55, 2.49)
Lymphocytes (%)	15.50 (10.05, 50.25)	11.10 (6.00, 19.50)

Table 1 continued

	Neonatal listeriosis	Non-neonatal listeriosis
Monocytes (%)	7.80 (4.25, 13.00)	5.15 (3.90, 7.00)
Eosinophils (%)	0.64 (0.00, 1.90)	0.00 (0.00, 0.20)
Basophils (%)	0.02 (0.00, 0.98)	0.00 (0.00, 0.20)
Platelet ($\times 10^9$/l)	153 (118, 221)	198 (154, 234)
RBC ($\times 10^{12}$/l)	4.06 ± 0.33	3.84 ± 0.78
Hemoglobin (g/l)	148.8 ± 16.95	116.2 ± 22.35
Liver function		
ALT (U/l)	18.00 (8.50, 29.75)	27.00 (15.00, 46.00)
AST (U/l)	71.50 (53.50, 163.3)	27.00 (18.00, 41.00)
T-BIL (μmol/l)	41.64 (32.87, 51.18)	11.90 (8.51, 17.69)
Total protein (g/l)	47.28 ± 10.26	59.81 ± 9.01
Albumin (g/l)	29.14 ± 5.13	32.42 ± 5.69
Globulin (g/l)	18.14 ± 6.18	27.34 ± 5.93
Renal function		
Urea nitrogen (mmol/l)	3.06 (2.18, 3.79)	3.69 (2.42, 5.90)
Creatinine (μmol/l)	59.00 (47.75, 89.30)	51.30 (38.80, 64.00)
Uric acid (μmol/l)	259.5 (155.3, 324.9)	174.0 (142.0, 265.0)
Electrolyte		
K^+ (mmol/l)	4.71 ± 1.02	3.70 ± 0.47
Na^+ (mmol/l)	135.8 ± 4.83	134.7 ± 6.56
Cl^- (mmol/l)	102.1 ± 5.48	101.3 ± 7.50
Ca^{2+} (mmol/l)	2.11 ± 0.65	2.10 ± 0.20
Blood glucose (mmol/l)	2.42 (1.52, 3.15)	5.64 (4.31, 8.05)
CRP (mg/l)	41.62 (32.00, 62.00)	52.84 (18.30, 107.5)
Procalcitonin (μg/l)	13.78 (4.91, 35.65)	0.30 (0.12, 0.99)

AIDS acquired immunodeficiency syndrome, *WBC* white blood cells, *RBC* red blood cells, *ALT* alanine aminotransferase, *AST* aspartate aminotransferase, *T-BIL* total bilirubin, *CRP* C-reactive protein

postpartum, which were the results of *L. monocytogenes* infections in the third trimester of pregnancy. The characteristics of maternal-neonatal listeriosis are shown in Table 2. These five neonatal listeriosis cases suffered with fetal distress and sepsis. Three neonatal cases with severe complications, such as respiratory

Table 2 Clinical characteristics of maternal-neonatal listeriosis

	Maternal case 1	Neonatal case 1	Maternal case 2	Neonatal case 2	Maternal case 3	Neonatal case 3	Maternal case 4	Neonatal case 4	Maternal case 5	Neonatal case 5
Age	32 years	1 day	31 years	1 day	31 years	1 day	30 years	1 day	29 years	1 day
Sex	Female	Female	Female	Male	Female	Female	Female	Female	Female	Female
Gestation	31 weeks		35 weeks		34 weeks		30 weeks		38 weeks	
Type of listeriosis	Bacteremia	Bacteremia	Bacteremia	Bacteremia	Bacteremia	Bacteremia	Bacteremia	Neurolisteriosis	Bacteremia	Bacteremia
Presentation	Fever	Fetal distress, sepsis	Decreased fetal movement	Fetal distress, septic shock, neonatal necrotizing enterocolitis, intubation	Fever, abdominal pain	Fetal distress, sepsis	Fever, cough	Fetal distress, respiratory failure, septic shock, diffuse intravascular coagulation, cerebral edema, intubation	Abdominal pain	Fetal distress, sepsis, respiratory failure
WBC ($\times 10^9$/l)	15.56	1.88	16.76	12.12	24.05	9.49	19.23	4.08	22.84	16.53
Platelet ($\times 10^9$/l)	154	87	214	154	216	128	182	83	175	114
RBC ($\times 10^{12}$/l)	3.35	4.07	3.30	3.78	4.33	4.04	4.13	3.88	4.64	4.42
Hemoglobin (g/l)	106	172	98	138	109	151	116	151	130	167
CRP (mg/l)	194	40	128	41.62	59	32	18	51	135	28.16

Table 2 continued

	Maternal case 1	Neonatal case 1	Maternal case 2	Neonatal case 2	Maternal case 3	Neonatal case 3	Maternal case 4	Neonatal case 4	Maternal case 5	Neonatal case 5
Procalcitonin (μg/l)	1.01	< 0.05	3.68	23.12	0.23	19.52	< 0.05	35	0.49	37.58
Culture sites	Placenta	Blood, laryngeal swab	Placenta	Blood, cochlear swab	Placenta	Blood, cochlear swab	Blood	Blood, cochlear swab, tracheal tube tip	Placenta	Blood, laryngeal swab
Antibiotic	Piperacillin/tazobactam	Meropenem	Piperacillin/tazobactam	Piperacillin/tazobactam	Penicillin	Penicillin	Penicillin	Penicillin	Penicillin	Meropenem + penicillin
Outcome	Recovered	Survived	Recovered	Decreased on day 3	Recovered	Survived	Recovered	Decreased on day 6	Recovered	Decreased on day 2

WBC white blood cells, *RBC* red blood cells, *CRP* C-reactive protein

failure and septic shock, decreased in less than 1 week (Table 2).

Characteristics of Bacteremia and Neurolisteriosis

There were 43 cases of bacteremia and 28 cases of neurolisteriosis identified. Sixteen cases of neurolisteriosis were isolated or detected *L. monocytogenes* from blood. Bacteremia listeriosis had a higher survival rate (88%) compared with neurolisteriosis (64%) (Table 3). There were no statistically significant differences in the levels of indicators for blood routine test, CRP, or procalcitonin between bacteremia and neurolisteriosis ($P > 0.05$, Table 3). Bacteremia listeriosis had lower levels of total protein, albumin, and urea nitrogen but higher levels of uric acid and chloride compared with neurolisteriosis ($P < 0.05$, Table 3). Neurolisteriosis revealed elevated blood glucose levels, which were higher than the upper limit of normal and significantly higher than in bacteremia ($P < 0.001$, Table 3).

Twenty-six neurolisteriosis received lumbar puncture. Twenty-five cases had abnormal appearance (turbid) and/or color (yellow) of CSF. Sixteen patients (62%) had elevated CSF pressure with median level of 240 (135, 300) mmH_2O. However, the CSF pressure in the death cases was lower than in survival case of neurolisteriosis [128 (103, 247) mmH_2O vs. 270 (185, 335) mmH_2O, $P = 0.022$]. Pyocytes were detected in CFS in two neurolisteriosis. The total cell count in CSF was 522 (360, 746) $\times 10^6$/l, while the WBC count in CSF was 429 (288, 674) $\times 10^6$/l, which were significantly elevated than upper limits of normal. The median percentage of polymorphonuclear cells in CSF was 62.50 (28.75, 70.00)%, while the median percentage of mononuclear cells in CSF was 37.50 (30.00, 71.25)%. All 26 neurolisteriosis cases had robustly elevated protein level in CSF [2046 (809.1, 5630) mg/l]. The median CSF glucose [3.09 (1.39, 5.88) mmol/l] and chloride (112.0 ± 8.99 mmol/l) level was remarkably down-regulated. There were no significant differences in laboratory indicators of CSF between survival and death cases of neurolisteriosis ($P > 0.05$). Twenty-five neurolisteriosis patients received cranial imaging

Table 3 Comparison of clinical characteristics between bacteremia and neurolisteriosis

	Bacteremia	Neurolisteriosis	*P* value
Case (*n*)	43	28	–
Age (range)	20 min ~ 75 years	8 h ~ 78 years	0.006
Male gender (*n*, %)	10 (23%)	18 (64%)	0.001
Female gender (*n*, %)	33 (77%)	10 (36%)	
Survive (*n*, %)	38 (88%)	18 (64%)	0.015
Death (*n*, %)	5 (12%)	10 (36%)	
Isolation or detection of *Listeria monocytogenes* from blood	43 (100%)	16 (57%)	< 0.001
Blood routine test			
WBC ($\times 10^9$/l)	14.76 (7.45, 20.44)	10.45 (5.79, 15.54)	0.066
Neutrophils (%)	74.99 ± 16.24	80.87 ± 11.73	0.104
Lymphocytes (%)	14.85 (7.75, 23.15)	9.70 (6.08, 15.93)	0.189
Monocytes (%)	5.00 (4.00, 7.70)	5.45 (3.40, 8.43)	1.000
Eosinophils (%)	0.00 (0.00, 0.40)	0.00 (0.00, 0.28)	0.440
Basophils (%)	0.00 (0.00, 0.20)	0.10 (0.00, 0.18)	0.285
Platelet ($\times 10^9$/l)	182 (129, 226)	190 (144, 261)	0.410
RBC ($\times 10^{12}$/l)	3.75 ± 0.79	4.07 ± 0.59	0.071
Hemoglobin (g/l)	118.3 ± 25.95	127.0 ± 22.06	0.149
Liver function			
ALT (U/l)	20.00 (13.00, 44.00)	32.50 (17.50, 55.00)	0.083
AST (U/l)	30.00 (20.00, 62.00)	31.50 (21.25, 56.50)	0.576
T-BIL (μmol/l)	12.60 (7.40, 27.30)	15.16 (10.72, 26.50)	0.320
Total protein (g/l)	55.04 ± 10.01	61.76 ± 9.54	0.006
Albumin (g/l)	30.24 ± 5.83	34.36 ± 4.56	0.002
Globulin (g/l)	24.74 ± 6.45	27.40 ± 7.29	0.110
Renal function			
Urea nitrogen (mmol/l)	2.74 (2.06, 4.76)	4.72 (3.13, 7.49)	< 0.001
Creatinine (μmol/l)	50.90 (38.80, 59.00)	56.40 (44.08, 82.55)	0.083
Uric acid (μmol/l)	229.6 (151.0, 276.0)	152.9 (113.2, 260.3)	0.048
Electrolyte			
K^+ (mmol/l)	3.97 ± 0.80	3.71 ± 0.47	0.120
Na^+ (mmol/l)	135.8 ± 5.37	133.3 ± 7.31	0.101

Table 3 continued

	Bacteremia	Neurolisteriosis	*P* value
Cl^- (mmol/l)	102.8 ± 6.77	99.37 ± 7.40	0.049
Ca^{2+} (mmol/l)	2.13 ± 0.33	2.07 ± 0.29	0.486
Blood glucose (mmol/l)	4.35 (3.18, 5.31)	7.67 (5.73, 9.51)	< 0.001
CRP (mg/l)	59.11 (29.04, 98.67)	37.81 (14.63, 114.9)	0.264
Procalcitonin (μg/l)	0.23 (0.11, 1.35)	0.71 (0.20, 2.10)	0.143

AIDS acquired immunodeficiency syndrome, *WBC* white blood cells, *RBC* red blood cells, *ALT* alanine aminotransferase, *AST* aspartate aminotransferase, *T-BIL* total bilirubin, *CRP* C-reactive protein

examinations (computed tomography and/or magnetic resonance imaging). Fifteen patients had abnormal cranial imaging. Eleven cases presented as cerebral edema/hydrocephalus (two patients underwent lateral ventricular drainage), five cases revealed intracranial infection, and three patients showed cerebral hernia. All neurolisteriosis death cases had cerebral edema/hydrocephalus or hernia.

Antibiotic Susceptibility and Therapeutic Strategy

Fifty-nine cases were positive for *L. monocytogenes* of blood culture, and 18 cases were positive for *L. monocytogenes* of CSF culture. Antibiotic susceptibility test for 59 of *L. monocytogenes* isolates from blood showed that one isolate was resistant to ampicillin, one resistant to penicillin, two resistant and two non-sensitive to meropenem, two resistant and one non-sensitive to trimethoprim-sulfonamide (SMZ), one resistant and five non-resistant to erythromycin. Antibiotic susceptibility test for 18 of *L. monocytogenes* isolates from CSF revealed that no isolates were resistant to ampicillin, one intermediate to penicillin, one non-sensitive to meropenem, one resistant to SMZ, one intermediate and seven non-resistant to erythromycin. Thirty-nine patients were administrated ampicillin or penicillin-based therapy. Fifteen patients received meropenem-based therapy. Fifteen patients received piperacillin/tazobactam treatment. Two cases, who received empirical ceftriaxone therapy, unfortunately died before obtaining antibiotic susceptibility test results.

Fatality Risk Factors for Listeriosis Patients

A total of 56 listeriosis patients survived in response to therapy, but 15 patients died due to *L. monocytogenes* infection. The death group had a higher ratio of male patients (73 vs. 30%, $P = 0.002$, Table 4), and elevated T-BIL level compared with survival group ($P = 0.017$, Table 4). Although the death group had increased levels of eosinophils percentage, hemoglobin, AST, urea nitrogen, Ca^{2+}, procalcitonin, but decreased Cl^- level, these differences just missed statistical significance (Table 4).

We firstly included all enrolled subjects (both non-neonatal and neonatal listeriosis) to analyze the fatality risk factors. The results showed that male gender (OR 4.83; 95% CI 1.08–21.56; $P = 0.039$), neurolisteriosis (OR 6.03; 95% CI 1.33–27.22; $P = 0.020$), T-BIL (OR 6.03; 95% CI 1.33–27.22; $P = 0.020$), and uric acid (OR 5.14; 95% CI 1.17–22.61; $P = 0.030$) presented an increased fatality risk in the univariate model (Table 5). After adjusting for age, gender, neurolisteriosis, blood routine, liver and kidney function indicators, electrolytes, blood glucose, CRP, and procalcitonin, we found that neurolisteriosis (OR 10.88; 95% CI 1.61–73.53; $P = 0.014$) and T-BIL (OR 13.74; 95% CI 1.85–101.94; $P = 0.010$) increased the fatality risk (Table 4). However, Na^+ showed a reduced fatality risk in the multivariate-adjusted regression analysis (OR 0.10; 95% CI 0.01–0.82; $P = 0.032$) (Table 5). We

Table 4 Comparison of clinical characteristics between the survival and death groups

	Survival group	Death group	*P* value
Case (*n*)	56	15	–
Age (range)	8 h ~ 78 years	20 min ~ 78 years	0.371
Male gender (*n*, %)	17 (30%)	11 (73%)	0.002
Female gender (*n*, %)	39 (70%)	4 (27%)	
Bacteremia (*n*, %)	38 (68%)	5 (33%)	0.015
Neurolisteriosis (*n*, %)	18 (32%)	10 (67%)	
Underlying diseases (*n*, %)	15 (27%)	8 (53%)	0.101
Blood routine test			
WBC ($\times 10^9$/l)	13.13 (7.29, 18.92)	11.80 (4.76, 16.05)	0.251
Neutrophils (%)	77.72 ± 13.05	75.98 ± 20.51	0.690
Lymphocytes (%)	12.00 (7.00, 21.00)	12.10 (6.30, 42.00)	0.678
Monocytes (%)	5.80 (4.00, 8.10)	5.30 (2.90, 7.60)	0.394
Eosinophils (%)	0.00 (0.00, 0.20)	0.20 (0.00, 1.60)	0.060
Basophils (%)	0.00 (0.00, 0.10)	0.00 (0.00, 0.30)	0.474
Platelet ($\times 10^9$/l)	198 (133, 232)	170 (148, 264)	0.949
RBC ($\times 10^{12}$/l)	3.85 ± 0.78	4.00 ± 0.47	0.495
Hemoglobin (g/l)	118.8 ± 24.79	132.7 ± 21.72	0.052
Liver function			
ALT (U/l)	24.50 (14.25, 36.75)	35.00 (14.00, 58.00)	0.430
AST (U/l)	27.00 (20.00, 49.50)	52.00 (24.00, 82.00)	0.054
T-BIL (μmol/l)	11.90 (8.28, 23.21)	26.60 (14.42, 32.59)	0.017
Total protein (g/l)	57.75 ± 9.63	57.46 ± 12.89	0.923
Albumin (g/l)	31.73 ± 5.80	32.35 ± 5.49	0.712
Globulin (g/l)	25.97 ± 6.32	25.11 ± 8.84	0.669
Renal function			
Urea nitrogen (mmol/l)	3.20 (2.24, 4.85)	5.37 (3.10, 7.45)	0.060
Creatinine (μmol/l)	51.74 (39.18, 62.25)	57.80 (46.30, 92.00)	0.101
Uric acid (μmol/l)	205.0 (148.6, 272.9)	148.5 (98.00, 272.4)	0.228
Electrolyte			
K^+ (mmol/l)	3.80 ± 0.70	4.11 ± 0.66	0.129
Na^+ (mmol/l)	135.1 ± 6.13	133.8 ± 6.94	0.455
Cl^- (mmol/l)	102.2 ± 6.58	98.64 ± 8.74	0.089

Table 4 continued

	Survival group	Death group	*P* value
Ca^{2+} (mmol/l)	2.07 ± 0.32	2.23 ± 0.27	0.087
Blood glucose (mmol/l)	5.00 (3.81, 7.15)	7.65 (3.12, 9.05)	0.603
CRP (mg/l)	59.11 (20.63, 114.0)	37.81 (16.40, 48.82)	0.137
Procalcitonin (μg/l)	0.300 (0.12, 1.04)	1.12 (0.28, 14.80)	0.073

AIDS acquired immunodeficiency syndrome, *WBC* white blood cells, *RBC* red blood cells, *ALT* alanine aminotransferase, *AST* aspartate aminotransferase, *T-BIL* total bilirubin, *CRP* C-reactive protein

then separately analyzed the fatality risk factors for non-neonatal and neonatal listeriosis. Age (OR 1.07; 95% CI 1.01–1.14; $P=0.030$), male gender (OR 10.38; 95% CI 1.10–98.20; $P=0.041$), neurolisteriosis (OR 11.67; 95% CI 1.23–110.80; $P=0.032$), immunosuppression (OR 8.00; 95% CI 1.24–51.68; $P=0.029$) and uric acid (OR 11.33; 95% CI 1.68–76.26; $P=0.013$) revealed an increased fatality risk of non-neonatal listeriosis in the univariate model (Table 6). After adjusting for age, gender, neurolisteriosis, blood routine, liver and kidney function indicators, electrolytes, blood glucose, CRP, and procalcitonin, uric acid (OR 11.33; 95% CI 1.68–76.26; $P=0.013$) elevated the fatality risk in non-neonatal listeriosis (Table 6). However, no correlates of the risk of neonatal listeriosis fatality were observed (Table 7).

DISCUSSION

In this retrospective study, we found that listeriosis was sporadic in Xi'an from 2011 to 2023, without the evidence of an outbreak. Similar to the previous reports [19–21], *L. monocytogenes* infection predominantly manifested as bacteremia (61%), while others presented as central nervous system infection (39%). The current study involved 23 maternal *L. monocytogenes* infections, leading to the predominance of female cases (61%), which was different to the large-scale analyses in China [19–21]. The total fatality rate was 21% (15/71), which was similar to the published retrospective reviews in China by Chen et al. in total infected population (18%) [19] and by Fan et al. in non-perinatal listeriosis (24%) [21]. The overall case fatality rate was notably lower than the international average rate of 30% [23]. It was shown that the evolution rate of *L. monocytogenes* was lower, leading to a specific geographical distribution of *L. monocytogenes* [24]. Although we did not perform the molecular characterization analysis of *L. monocytogenes* isolates, the lower fatality rate in Xi'an and other cities in China might be associated with the differences in predominance of serogroup, sequence types, and clone complexes between *L. monocytogenes* strains in China and other countries/regions [25–27]. *L. monocytogenes* infections analyzed in this study revealed that human listeriosis in Xi'an was mainly concentrated in spring and summer, which was related to the transmission feature of food-borne disease by contaminated food. The similar seasonal variation has been observed in other Chinese studies [19, 21], which might be the seasonal pattern of listeriosis in China. The prevalence of *L. monocytogenes* in food products in Shaanxi province was 11%, which was the highest value and significantly higher than the average prevalence of 4.42% in Chinese food products from 28 provinces [28]. However, only one non-neonatal case in this analysis confirmed the history of contaminated food ingestion. This might be due to the fact that listeriosis was characterized by a wide spectrum of infections and *L. monocytogenes* infection has a long incubation period, resulting in the difficulty in tracking an accurate food eating history [5]. Thus, listeriosis can be easily misdiagnosed in clinical practice. It is also important to understand the clinical features of *L. monocytogenes* infection for a timely diagnosis of listeriosis.

Table 5 Logistic regression analysis of factors influencing the clinical outcome of all enrolled subjects

Characteristics	Univariate model		Multivariate model	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Age	0.99 (0.96–1.03)	0.720		
Male gender	4.83 (1.08–21.56)	0.039		
Neurolisteriosis	6.03 (1.33–27.22)	0.020	10.88 (1.61–73.53)	0.014
Immunosuppression	2.92 (0.66–12.81)	0.156		
Underlying diseases	2.31 (0.57–9.36)	0.242		
Blood routine test				
WBC count	0.34 (0.08–1.51)	0.156		
Neutrophils percentage	99.99 (0.01–99.99)	0.963		
Lymphocytes percentage	99.99 (0.01–99.99)	0.957		
Monocytes percentage	2.07 (0.51–8.35)	0.306		
Eosinophils percentage	0.24 (0.04–1.31)	0.099		
Basophils percentage	99.99 (0.01–99.99)	0.982		
Platelet count	2.20 (0.46–10.66)	0.326		
RBC count	0.89 (0.20–3.96)	0.876		
Hemoglobin	1.02 (0.25–4.16)	0.978		
Liver function				
ALT	1.94 (0.46–8.18)	0.367		
AST	3.46 (0.83–14.36)	0.087		
T-BIL	6.03 (1.33–27.22)	0.020	13.74 (1.85–101.94)	0.010
Total protein	0.65 (0.16–2.60)	0.547		
Albumin	1.13 (0.25–5.02)	0.876		
Globulin	3.30 (0.79–13.75)	0.101		
Renal function				
Urea nitrogen	1.73 (0.32–9.31)	0.521		
Creatinine	0.35 (0.07–1.83)	0.213		
Uric acid	5.14 (1.17–22.61)	0.030		
Electrolyte				
K^+	0.26 (0.03–2.24)	0.218		
Na^+	0.41 (0.09–1.79)	0.236	0.10 (0.01–0.82)	0.032
Cl^-	1.53 (0.38–6.09)	0.547		
Ca^{2+}	0.40 (0.09–1.71)	0.216		

Table 5 continued

Characteristics	Univariate model		Multivariate model	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Blood glucose	99.99 (0.01–99.99)	0.944		
CRP	0.92 (0.09–9.28)	0.946		
Procalcitonin	1.72 (0.43–6.99)	0.445		

WBC white blood cells, *RBC* red blood cells, *ALT* alanine aminotransferase, *AST* aspartate aminotransferase, *T-BIL* total bilirubin, *CRP* C-reactive protein

A total of 35 cases of *L. monocytogenes* infections (23 maternal and 12 neonatal listeriosis) during perinatal period were reported in this study, accounting for 49% cases in overall studied patients. All maternal patients presented as bacteremia without the involvement of central nervous system infection. The main symptom was fever, and no cases of death were reported. This was consistent with the previous findings that listeriosis in pregnancy usually revealed non-specific, influenza-like clinical presentation with a low fatality rate [7, 8, 29–31]. Although most maternal listeriosis showed mild febrile illness, the laboratory testing results revealed remarkably higher WBC counts and CRP levels in this study, indicating the strong inflammatory response in *L. monocytogenes*-infected pregnant women. This might be the reason that maternal listeriosis always leads to adverse pregnancy outcomes. Although all maternal listeriosis cases accepted proposals for sensitive antibiotics therapy, 65% (15/23) had abortions due to listeriosis because these patients revealed the histopathological and/or micrological-proven *L. monocytogenes* infection in the placenta. Eight cases had singleton live births, but five of them delivered culture-positive neonates. Three maternal listeriosis patients who delivered uninfected neonates received penicillin therapy, which might prevent direct transmission of infection to the fetus or neonate. Taken together with other published literature [7, 8, 13, 29–31], maternal listeriosis could induce devastating consequences for the fetus and newborns. All 12 enrolled neonatal listeriosis cases were identified as early onset infection, and the most common symptom was fetal distress with the fatality rate of 42% (5/12). The WBC count was slightly increased, but the procalcitonin level was robustly elevated. This was in line with the findings in clinical features of neonatal *L. monocytogenes* infection reported in China [30, 31]. However, the fatality rate was still higher than the *L. monocytogenes*-infected newborns in France [9] and other early onset bacterial infection in term infants [32], owing to the intrapartum antibiotic prophylaxis only in high-risk pregnant women.

A total of 36 cases of non-maternal adult listeriosis were reported in this study, accounting for 51% of cases in the overall enrolled patients. Two-thirds of non-maternal listeriosis patients were neurolisteriosis. Invasive *L. monocytogenes* infection mainly affected non-maternal individuals with immunocompromised conditions [33]. The MONALISA perspective study in France showed that 97% of bacteremia listeriosis cases had underlying diseases, including neoplasm, diabetes, or were receiving immunosuppressive therapy [13]. Neurolisteriosis also mainly occurred in the elderly and immunocompromised patients [1, 34, 35]. A retrospective study in the Netherlands revealed that *L. monocytogenes* infection accounted for approximately 16% of community-acquired bacterial meningitis in patients 80 years or older [36]. The symptoms of non-maternal listeriosis included fever (85–90%) patients and disorder of consciousness (20%) [13, 37]. In this study, the average age of non-maternal listeriosis was > 50 years, and > 60% patients (22 cases) had underlying diseases. Among them, 17 cases underwent immunocompromised conditions, including steroid administration (seven cases), chemotherapy (nine cases), and AIDS (one case). Only one patient met the criteria of "healthcare-associated case", which was defined as an onset of

Table 6 Logistic regression analysis of factors influencing clinical outcome of non-neonatal listeriosis

Characteristics	Univariate model		Multivariate model	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Age	1.07 (1.01–1.14)	0.030		
Male gender	10.38 (1.10–98.20)	0.041		
Maternal listeriosis	0.01 (0.01–99.99)	0.936		
Neurolisteriosis	11.67 (1.23–110.80)	0.032		
Tumor	3.80 (0.29–49.91)	0.310		
Diabetes	0.01 (0.01–99.99)	0.982		
Immunosuppression	8.00 (1.24–51.68)	0.029		
Underlying diseases	4.15 (0.67–25.68)	0.126		
Blood routine test				
WBC count	0.18 (0.03–1.09)	0.062		
Neutrophils percentage	99.99 (0.01–99.99)	0.974		
Lymphocytes percentage	99.99 (0.01–99.99)	0.964		
Monocytes percentage	2.33 (0.41–13.26)	0.339		
Eosinophils percentage	0.26 (0.02–3.46)	0.310		
Platelet count	2.36 (0.36–15.50)	0.372		
RBC count	2.08 (0.37–11.74)	0.408		
Hemoglobin	0.68 (0.11–4.13)	0.672		
Liver function				
ALT	5.27 (0.84–32.99)	0.076		
AST	1.50 (0.24–9.46)	0.666		
T-BIL	3.44 (0.59–20.10)	0.169		
Total protein	0.15 (0.02–1.38)	0.094		
Albumin	0.54 (0.10–3.03)	0.482		
Globulin	0.94 (0.09–9.37)	0.960		
Renal function				
Urea nitrogen	1.90 (0.20–18.11)	0.578		
Creatinine	0.61 (0.10–3.73)	0.593		
Uric acid	11.33 (1.68–76.26)	0.013	11.33 (1.68–76.26)	0.013
Electrolyte				
K^+	0.47 (0.05–4.43)	0.507		
Na^+	0.50 (0.08–3.05)	0.452		

Table 6 continued

Characteristics	Univariate model		Multivariate model	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Cl^-	2.71 (0.44–16.52)	0.281		
Ca^{2+}	1.25 (0.13–12.25)	0.848		
Blood glucose	99.99 (0.01–99.99)	0.953		
CRP	0.56 (0.05–6.02)	0.629		
Procalcitonin	0.68 (0.11–4.13)	0.672		

WBC white blood cells, *RBC* red blood cells, *ALT* alanine aminotransferase, *AST* aspartate aminotransferase, *T-BIL* total bilirubin, *CRP* C-reactive protein

listeriosis symptoms more than 48 h post admission for medical conditions other than listeriosis [22]. This bacteremia listeriosis case was diagnosed as multiple myeloma, and received stem cells transplantation. This patient suffered from a sudden onset of high fever 4 days post transplantation, with WBC count only 0.03×10^9/l. Previous findings show that only 40% neurolisteriosis patients had the classical triad of bacterial meningitis as fever, neck stiffness, and a change in mental status [1, 37–39]. Neurolisteriosis patients also typically present with a slow onset of symptoms, with a lesser extent elevation of CSF leukocyte counts, high CSF level, and low CSF to blood glucose ratio [13, 37]. The main neuroradiological images are meningeal enhancement, abscess, hemorrhages, contrast-enhancing ventricles, or hydrocephalus [40, 41]. The clinical characteristics of neurolisteriosis cases enrolled in this study matched all the above features. Thus, when the patients with underlying diseases or in the immunocompromised conditions suffered from clinical symptoms of fever or central nervous system infection, they should be alert to the possibility of listeriosis. Early administration of ampicillin- or penicillin-based therapeutic strategy might be beneficial in clinical recovery of listeriosis.

Due to the limited enrolled subjects of the current study, we divided all patients into bacteremia and neurolisteriosis. Although neurolisteriosis seemed to have a higher fatality rate than bacteremia, only urea nitrogen and blood glucose revealed statistically significant differences between the two groups. Thus, we attempted to seek the risk factors associated with death in all cases with invasive *L. monocytogenes* infection. Niu et al. showed that consumption of Chinese cold dishes increased the risk of *L. monocytogenes* infection by 3.43-fold in Beijing, China [42]. The MONALISA perspective study indicated that the strongest fatality predictors for bacteremia and neurolisteriosis were ongoing cancer, multi-organ failure, aggravation of pre-existing organ dysfunction, and monocytopenia [13]. A Spanish retrospective study also showed that the main factors associated with early fatality (less than 5 years) after recovery were age and with the comorbidities of diabetes, chronic kidney disease, liver disease, and cancer [43]. Herein, our present data showed that neurolisteriosis and elevated T-BIL increased the fatality risk, but serum sodium level showed a reduced fatality risk in all enrolled subjects. This indicated that the risk factors of fatality for listeriosis were the involvement of central nervous system, hyperbilirubinemia, and hyponatremia in all enrolled subjects. It was also well accepted that craniocerebral injury caused by trauma or meningitis always resulted in hyperkalemia, which contributed to the elevation of fatality rate [44]. Although we did not find statistically significant differences of serum potassium levels between the survival and death cases, the serum potassium level should be monitored, especially in neurolisteriosis. Hyperbilirubinemia increased the risk of infection in the surgical intensive care unit even though the sepsis-related jaundiced patients were excluded [45]. Hyponatremia also reflected the severity of the underlying process,

Table 7 Logistic regression analysis of factors influencing clinical outcome of neonatal listeriosis

Characteristics	Univariate model	
	OR (95% CI)	*P* value
Male gender	2.00 (0.09–44.35)	0.661
Neurolisteriosis	99.99 (0.01–99.99)	0.952
Blood routine test		
WBC count	6.00 (0.22–162.53)	0.287
Neutrophils percentage	99.99 (0.01–99.99)	0.948
Monocytes percentage	0.50 (0.02–11.09)	0.661
Eosinophils percentage	2.00 (0.09–44.35)	0.661
Basophils percentage	99.99 (0.01–99.99)	0.967
Platelet count	99.99 (0.01–99.99)	0.967
RBC count	0.01 (0.01–99.99)	0.966
Hemoglobin	99.99 (0.01–99.99)	0.952
Renal function		
Urea nitrogen	6.00 (0.22–162.53)	0.287
Uric acid	0.67 (0.03–18.06)	0.810
Electrolyte		
K^+	0.01 (0.01–99.99)	0.966
Na^+	0.17 (0.01–4.52)	0.287
Cl^-	99.99 (0.01–99.99)	0.967
Ca^{2+}	0.17 (0.01–4.52)	0.287

WBC white blood cells, *RBC* red blood cells, *ALT* alanine aminotransferase, *AST* aspartate aminotransferase, *T-BIL* total bilirubin, *CRP* C-reactive protein

although it did not induce specific symptoms and might be overlooked by clinicians [46]. Of note, Shuaib et al. revealed that hyperbilirubinemia and hyponatremia yielded a discriminatory value for the diagnosis of complicated appendicitis [47]. Thus, T-BIL and serum sodium levels can be considered as adjuvant predictors of poor clinical outcomes in neurolisteriosis in all enrolled subjects. We further separately analyzed the fatality risk factors for neonatal and non-neonatal listeriosis because the neonates had different backgrounds in anatomy, physiology, and biochemistry with adults. We found that no correlates of the risk of neonatal listeriosis fatality were observed. In our point of view, the limited enrolled number ($n=12$) probably contributed to this negative result. Interestingly, hyperuricemia contributed to the elevation of fatality risk in non-neonatal listeriosis. Previous reports revealed that hyperuricemia was associated with increased risk of 90-day all-cause mortality and the incidence of acute kidney injury in patients with sepsis [48]. High uric acid levels were also associated with adverse outcomes in patients hospitalized for coronavirus disease 2019 [49]. Thus, we suggested that evaluating hyperuricemia as a potential marker might reflect poor prognostic baseline characteristics in non-neonatal listeriosis.

There were several limitations in this study. On the one hand, due to the limited sample size, the interpretation of the current findings still needs further elucidation in a larger-scale cohort. On the other hand, *L. monocytogenes* infection is strongly associated with host immune status. We only described the immunocompromised conditions of the listeriosis patients, and objective clinical index reflecting immune conditions, such as $CD4^+/CD8^+$ T cell count and cytokine levels, should be investigated in these patients.

CONCLUSIONS

When patients suffer from symptoms of fever or central nervous system infection, they should be alert to the possibility of listeriosis. The main risk factors for death due to listeriosis are the involvement of the central nervous system, hyperbilirubinemia, and hyponatremia. Early administration of ampicillin- or penicillin-based therapy might be beneficial for recovery of listeriosis.

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Data Availability. The datasets generated during and analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Conflict of Interest. Wen Xu, Mei-Juan Peng, Lin-Shan Lu, Zhen-Jun Guo, A-Min Li, Jing Li, Yan Cheng, Jia-Yu Li, Yi-Jun Li, Jian-Qi Lian, Yu Li, Yang Sun, Wei-Lu Zhang, and Ye Zhang declare that they have no competing interests.

Ethical Approval. The study protocol was approved by the Institutional Review Board of Tangdu Hospital (No. K202309-10), Shaanxi Provincial People's Hospital (No. 2023-0135), and The Second Affiliated Hospital of Xi'an Medical University (No. 23EC027). This study involving human participants was in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. We used an anonymized database for all analyses, and all potentially identifying variables were removed.

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