Original article

Epidemiology and Clinical Features of Patients with Tick Bites in the Japanese Spotted Fever-Endemic Zone

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ICMJE Statement

SF was the chief investigator and responsible for the data analysis. TS, OK, and YH designed the data collection format and performed data collection. HH supervised data analysis and manuscript. All authors contributed to the writing of the final manuscript.

ABSTRACT

Purpose: This study aimed to clarify the epidemiology and clinical features of tick bites in a Japanese spotted fever (JSF)-endemic area.

Method: The clinical records of patients with tick bites were retrospectively reviewed based on a survey conducted at Numakuma Hospital, Fukuyama City, Hiroshima, Japan, from 2016–2023. Data on basic characteristics, visit dates, residential address, exposure activities, tick-bite sites, and prophylactic antimicrobial prescriptions for each patient with tick bites were collected at the JSF hotspot hospital.

Results: A total of 443 patients with tick bites visited the hospital, of which data on 305 cases (68.8%) were reviewed. The median age of these patients was 71 years, with a higher proportion of women (63.0%). One-third of the patients had a preceding history of working in fields, whereas two-thirds had entered mountains or agricultural fields. Nearly 90% of the patients

visited the hospital from April to August, and the most common bite sites were the lower extremities (45.1%). Most patients (76.1%) resided in the southern area of Numakuma Hospital. Nearly all patients were prescribed prophylactic antibiotics (minocycline in 87.8% of cases), and none subsequently developed JSF.

Conclusion: Continued surveillance of patients with tick bites is warranted to better understand changes in the clinical impact of tick-borne diseases.

Keywords: global warming, Japanese spotted fever, tick bite, tick-borne diseases

Introduction

Tick species are ectoparasites and blood-sucking parasites of mammals, birds, and reptiles, which are recognized as important vectors for various infectious disease pathogens [1]. Recently, their epidemiological patterns have drastically changed because of global warming, and tick-borne diseases (TBDs) have become a major global concern [1–3]. Given that TBDs are transmitted through tick bites, extensive research and preventive interventions targeting tick exposure have been implemented to reduce incidence rates of TBDs [4]. In Japan, the representative TBDs include Tsutsugamushi disease, Japanese spotted fever (JSF), severe fever with thrombocytopenia syndrome (SFTS), anaplasmosis, and Lyme disease. Among these, JSF and SFTS are the most dominant in Western Japan [5,6].

JSF is caused by *Rickettsia japonica*, which was first reported in Japan in 1984 and is currently classified as a category IV infectious disease under the Act on the Prevention of Infectious Diseases and Medical Care for Patients with Infectious Diseases (the Infectious Diseases Control Law) [7,8]. Thereby, physicians are responsible for promptly notifying public health facilities upon diagnosing JSF. The reported case fatality rate of JSF ranges 2.0–3.3%, with potential progression to severe complications, including disseminated intravascular coagulation, multiple organ dysfunction syndrome, and meningoencephalitis [6,9–11]. To optimize patient outcomes through early therapeutic intervention, enhanced disease surveillance,

facilitating heightened awareness of disease epidemiology, are essential [9]. The number of JSF cases in Japan has increased approximately 10-fold over the past decade, rising from 0.03 cases per 100,000 population in 2001 to 0.33 cases per 100,000 population in 2020, with an average annual percentage change of 12.3% (95% confidential interval: 10.7–13.9) [5]. Notably, Hiroshima Prefecture has experienced an annual JSF increase rate of 38% in the past decade, making it as an endemic area in Japan [5]. Although prophylactic antibiotics for patients with tick bites may prevent the onset of JSF, they are not generally recommended in Japan because of the relatively low prevalence of TBDs [12]. Although public education on tick-bite protection is crucial to prevent JSF, detailed insights into the characteristics of populations affected by tick bites remain insufficient.

A previous study using the Japanese Diagnosis Procedure Combination Inpatient Database identified a hotspot zone located between the Hiroshima and Okayama Prefectures [6]. The authors, as infectious disease clinicians working in this region, hypothesized that patients with JSF would be predominantly located in and around Fukuyama City, Hiroshima, although no specific discussions or clear explanations for this high incidence have been provided. This study aimed to elucidate the epidemiology and clinical features of patients with tick bites in the JSF-endemic areas of Japan.

Methods

Numakuma Hospital, located on the outskirts of Fukuyama City in Japan (**Fig. 1**), is a secondary care facility with a total of 118 beds, including convalescent care beds. The hospital staff has conducted a tick-bite survey since 2016, and this retrospective observational study used their data on age, sex, date of visit, residential address, history of entering mountains or agricultural fields, tick-bite sites, and prophylactic antimicrobial prescriptions between 2016 and 2023. Tick-bite sites were classified into six categories; (1) head and neck, (2) chest, axilla, and back, (3) upper extremities, (4) abdomen and waist, (5) inguinal and perineum, and (6) lower extremities. Patients without clear records of the tick-bite sites were classified as unknown. A patient was defined as having a tick bite if a tick was found during the visit or brought in by themselves. The history of entering mountains or agricultural fields was based on patient self-reports. The estimated locations or occasions of tick bites were categorized as follows; field, mountain, grass cutting, home garden, animal-related, and unknown. Antibiotic prescriptions administered to patients with tick bites upon visit were also investigated.

Data for the new cases of JSF were obtained from the Infectious Diseases Weekly Report, Japan [13]. JSF is one of the notifiable diseases, classified under Category IV Infectious Diseases that should be immediately reported after diagnosis [8]. Thus, when patients with the disease are diagnosed, medical practitioners are responsible for informing the public health centers. The

reported data are then compiled by the National Epidemiologic Surveillance of Infectious Disease and made publicly available through an online platform [13]. To investigate the seasonality of the JSF onset, we collected incidence data from the 1st to the 52nd or 53rd week of each year between 2016 and 2022.

The requirement for informed consent was waived because this was a retrospective analysis of anonymized data. Ethical approval was obtained from the director of Numakuma Hospital.

Results

The incidence of JSF cases in Hiroshima Prefecture is depicted in **Fig. 2**. Between 2016 and 2022, Hiroshima Prefecture accounted for 13.0–22.3% of the total JSF cases in Japan. Throughout the year, the incidence of JSF begins to rise in April or May, both nationwide and in Hiroshima Prefecture, maintains a plateau, and reaches its peak around the 41st week in October. During the study period, 22 patients were diagnosed with JSF at Numakuma Hospital.

According to the tick-bite survey at Numakura Hospital, data were available for 443 cases, of which 305 cases (68.8%) were fully documented with detailed information based on previous medical interviews. Detailed data from 2016–2017 had been discarded five years after the record (57 cases), and from 2018 onwards, 81 cases were excluded due to data missing. Upon reviewing the survey data, the number of patients with tick bites visiting hospitals has nearly doubled

recently (**Fig. 3A**). Most tick-bite visits occurred between April and August (89.2%), with a peak from May to June (50.8%) (**Fig. 3B**).

The median age of the patients was 71 years (interquartile range [IQR], 52–90 years), and 37.0% were men (**Table 1**). Three-fourths of the patients (232 cases, 76.1%) resided in the southern area of the city. Based on medical interviews, the most likely scenario for tick bites was working in fields (35.7%), and 63.9% of patients had a history of entering mountains or agricultural fields. Of 305 patients, 283 cases (92.8%) received prophylactic antibiotic prescriptions. In most cases (258 adult cases), a 100 mg tablet of minocycline was administered twice daily, and none of these patients subsequently developed JSF. The duration of antibiotic treatment ranged from 1 to 10 days, with 227 out of 305 patients (74.4%) receiving a 7-day course of treatment. In contrast, the 22 patients diagnosed with JSF at Numakuma Hospital had no prior history of visiting the hospital for tick bites and did not receive the prophylactic antibiotics.

The tick-bite sites were detected in 178 patients (58.4%), whereas 41.6% of the patients had unknown bite sites because of missing data. The distribution of the identified tick-bite sites is shown in **Fig. 4**. The most common bite sites were the lower extremities (45.1%), followed by the upper extremities (17.0%), head and neck (11.5%), and thoracic and axillary regions (10.4%).

Discussion

We investigated the epidemiological and clinical characteristics of patients who visited the JSF hotspot hospital. The number of patients with tick bites visiting the hospital has increased, particularly among elderly women. Three-fourths of the patients resided in the southern area of Fukuyama City, with approximately 90% of cases occurring between April and August. The most likely situation for tick bites was working in fields (35.7%), with approximately 60% of tick-bite sites are in the limbs. Prophylactic antibiotics were prescribed to >90% of patients with tick bites at the hospital, and none of them subsequently developed JSF.

Global warming has expanded the habitats of ticks and increased their activity, making TBDs, including JSF, a global concern [2,5,14]. In England, the number of arthropod bites has been reported to be positively associated with temperature, with incidence rate ratios ranging from 1.03–1.14 between 2000 and 2013 [15]. An increase in tick bites undoubtedly poses a risk for TBDs worldwide [16–18]. In the United States, tick bites are commonly observed in patients aged 0–9 and 70–79 years, with a primary and secondary peak from April to July and October to November, respectively [16]. Although the tick species active in wild fields differ by country, their peak activities have consistently been reported in and around May [19,20]. Our data corroborate the seasonality of tick bite incidence, showing peaks in May and June as well. The incidence of JSF cases also increases during the spring season; however, its peak reaches in

October. The reason for this discrepancy remains unclear, although it may be related to the activity of the ticks that specifically transmit JSF. In Japan, *R. japonica* has been detected in tick species belonging to the genera *Dermacentor*, *Haemaphysalis*, and *Ixodes* [21,22]. In particular, *Haemaphysalis longicornis* demonstrates a high prevalence of spotted fever group rickettsiae, with a carrier rate of 62.8%, and also has been recognized as a high-risk vector of *R. japonica* [22,23]. However, the regional tick species distribution and their seasonal activity patterns in this geographical area remain undocumented. Further research and surveillance are needed to investigate the differences in seasonal peak incidences of tick bites and JSF cases in this JSF hotspot area.

Our data indicated an increasing trend in tick bite incidence over the past decade. Increased incidence of tick bites has been reported worldwide as well, including in the Netherlands [24] and France [25]. The increasing trend could be attributed to a greater likelihood of contact with ticks, resulting from a rise in the number of host animals [2,26,27]. Deer and wild boars are well-known vectors of *Rickettsia* species [28,29], and tick bites most commonly occur in fields where ticks are likely to be dropped by these wild animals. The extended survival and increased activity of ticks, driven by the expanding ranges of deer and wild boar, lead to a prolonged duration of human exposure to ticks [2]. According to the Ministry of the Environment, while the populations of these key animals are reportedly declining, their habitat areas are expanding and

overlapping with human habitation in Japan [30]. This fact is explainable for the increase in the tick bite incidence, and consequently, the number of JSF cases.

Being a woman over 50 years of age is a reported risk factor for tick bites [17], which was also indicated in the present study. Older individuals are generally considered at a higher risk of TBDs, as they are less likely to use insect repellent or check for ticks after potential exposure [31]. Other associated factors included spending time outdoors during the summer, educational level, ownership of domestic animals, hunting activities, and being a farmer [18,32]. Those who frequently venture into fields or mountains are especially at greater risk of tick bites; thus, we recommend that such high-risk populations should wear protective clothing that covers exposed skin, apply repellents, bathe or shower after outdoor activities, and thoroughly check themselves for tick bites.

Recently, the incidence of JSF is continuously increasing in Japan, especially among the older population [5]. Considering the rising trend in tick bites, the number of JSF cases is expected to further increase. For Lyme disease, the number needed to treat (prophylaxis, as in this case) is approximately 40 [33], and clinical practice guidelines recommend that prophylactic antibiotic therapy be administered to patients within 72 h of removal of a high-risk tick [34]. Although Fukuyama City is considered a representative endemic area for JSF [5,6], detailed epidemiological information needed to determine the necessity of antibiotic prophylaxis remains

unknown [12]. Surveys of tick-borne pathogens in other JSF-prevalent prefectures (Shizuoka, Mie, Wakayama, Kagoshima, Nagasaki, and Okinawa) have shown that 1.0% of ticks carry *Rickettsia japonica* [12]. However, Japanese guidelines for tick bites are yet to be established, and prophylactic antibiotics may often be prescribed owing to the lack of comprehensive epidemiological data. Further epidemiological data collection and continued surveillance of tick bites are necessary.

Our study has a significant strength in highlighting the epidemiological characteristics and clinical features of tick bites in the JSF-hotspot zone, which have rarely been reported in Japan. These data are crucial when proposing public health measures, such as tick prevention strategies. However, this study had several limitations. First, the information presented was based on a retrospective analysis of data collected at a single facility, and generalizability should be confirmed by other studies. Second, the effectiveness of the prophylactic antibiotic prescriptions could not be determined because of the absence of a comparative cohort. Patients presenting with tick bites were instructed to return to Numakuma Hospital if they developed pyrexia or cutaneous manifestations. While severe cases may have warranted transfer to tertiary care facilities, no patients returned with clinical manifestations of JSF. Although this observation might suggest potential prophylactic benefit of antimicrobial therapy, several limitations warrant consideration. Notably, the tick species responsible for exposure events were not identified,

despite the known variation in pathogen specificity among different tick vectors. Consequently, the efficacy of prophylactic antimicrobial administration following tick exposure in preventing JSF development remains undetermined in this investigation. Finally, data on patients who visited the hospital due to side effects were unavailable. The majority of cases underwent minocycline prescriptions, which can potentially result in side effects such as vomiting [35]. Disadvantages of prophylactic antibiotic administration include the risk of side effects, the potential for developing antimicrobial-resistant bacteria, and increased medical costs. The cost-benefit effectiveness of the prophylactic prescriptions for TBDs should be further investigated in Japan.

Collectively, we provided an overview of the epidemiological and clinical features of tick bites in a hotspot zone of JSF in Japan. Continued surveillance of tick bites and TBDs is required to address the effects of climate change. The advantages and disadvantages of prophylactic antibiotic prescription for patients with tick bites remain controversial. Further epidemiological and prospective comparative cohort studies are needed to resolve this issue.

Availability of data and materials

The datasets used in this study are available from the corresponding author upon request.

Competing interests

The authors declare no competing interests.

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None

Authors' contributions

SF drafted the manuscript. TS, OK, and YH collected the clinical data. HH revised the manuscript. All the authors interpreted the results and approved the submitted manuscript.

References

[1] Hoffman T, Olsen B, Lundkvist Å. The Biological and Ecological Features of Northbound Migratory Birds, Ticks, and Tick-Borne Microorganisms in the African-Western Palearctic. Microorganisms 2023;11.

[2] Bouchard C, Dibernardo A, Koffi J, Wood H, Leighton PA, Lindsay LR. N Increased risk of tick-borne diseases with climate and environmental changes. Can Commun Dis Rep 2019;45:83–9.

[3] Rochlin I, Toledo A. Emerging tick-borne pathogens of public health importance: a mini-review. J Med Microbiol 2020;69:781–91.

[4] Cuadera MKQ, Mader EM, Safi AG, Harrington LC. Knowledge, attitudes, and practices for tick bite prevention and tick control among residents of Long Island, New York, USA.

Ticks Tick Borne Dis 2023;14:102124.

[5] Otsuka Y, Hagiya H, Fukushima S, Harada K, Koyama T, Otsuka F. Trends in the Incidence of Japanese Spotted Fever in Japan: A Nationwide, Two-Decade Observational Study from 2001-2020. Am J Trop Med Hyg 2023;108:701–4.

[6] Ogawa T, Tsuzuki S, Ohbe H, Matsui H, Fushimi K, Yasunaga H, et al. Analysis of Differences in Characteristics of High-Risk Endemic Areas for Contracting Japanese Spotted Fever, Tsutsugamushi Disease, and Severe Fever With Thrombocytopenia Syndrome. Open Forum Infect Dis 2024;11:ofae025.

[7] Mahara F, Koga K, Sawada S, Taniguchi T, Shigemi F, Suto T, et al. [The first report of the rickettsial infections of spotted fever group in Japan: three clinical cases]. Kansenshogaku Zasshi 1985;59:1165–71.

[8] Ministry of Justice Act on the Prevention of Infectious Diseases and Medical Care for Patients with Infectious Diseases. Available at: https://www.japaneselawtranslation.go.jp/en/laws/view/2830/en. Accessed October 10, 2024.

[9] Sakabe S, Tanaka H, Nakanishi Y, Toyoshima H. The clinical course of 239 cases of Japanese spotted fever in Ise Red Cross Hospital, 2006-2019. J Infect Chemother 2022;28:211–6.

262 [10]Miyashima Y, Iwamuro M, Shibata M, Miyabe Y, Kawai Y, Kaihara M, et al. Prediction of
263 disseminated intravascular coagulation by liver function tests in patients with Japanese
264 spotted fever. Intern Med 2018;57:197–202.
265 [11]Nakata R, Motomura M, Tokuda M, Nakajima H, Masuda T, Fukuda T, et al. A case of
266 Japanese spotted fever complicated with central nervous system involvement and multiple
267 organ failure. Intern Med 2012;51:783–6.
268 [12]Gaowa, Ohashi N, Aochi M, Wuritu D, Wu, Yoshikawa Y, et al. Rickettsiae in ticks, Japan,
269 2007–2011. Emerg Infect Dis 2013;19:338–40.
270 [13]National Institute of Infectious Diseases, Japan. Available at:
271 https://www.niid.go.jp/niid/ja/tsls-m/2655-cepr/12718-stss-2024-06.html. Accessed October
272 10, 2024.
273 [14]Cui H, Shen S, Chen L, Fan Z, Wen Q, Xing Y, et al. Global epidemiology of severe fever
274 with thrombocytopenia syndrome virus in human and animals: a systematic review and
275 meta-analysis. Lancet Reg Health West Pac 2024;48:101133.
276 [15]Newitt S, Elliot AJ, Morbey R, Durnall H, Pietzsch ME, Medlock JM, et al. The use of
277 syndromic surveillance to monitor the incidence of arthropod bites requiring healthcare in
278 England, 2000-2013: a retrospective ecological study. Epidemiol Infect 2016;144:2251–9.
279 [16]Marx GE, Spillane M, Beck A, Stein Z, Powell AK, Hinckley AF. Emergency Department

Visits for Tick Bites - United States, January 2017-December 2019. MMWR Morb Mortal Wkly Rep 2021;70:612–6.

[17]Hjetland R, Eliassen KE, Lindbæk M, Nilsen RM, Grude N, Ulvestad E. Tick bites in healthy adults from western Norway: occurrence, risk factors, and outcomes. Ticks Tick Borne Dis 2013;4:304–10.

[18]Li S, Juhász-Horváth L, Trájer A, Pintér L, Rounsevell MDA, Harrison PA. Lifestyle, habitat and farmers' risk of exposure to tick bites in an endemic area of tick-borne diseases in Hungary. Zoonoses Public Health 2018;65:e248–53.

[19]Burtis JC, Bjork J, Johnson TL, Schiffman E, Neitzel D, Eisen RJ. Seasonal activity patterns of host-seeking Ixodes scapularis (Acari: Ixodidae) in Minnesota, 2015-2017. J Med Entomol 2023;60:769–77.

[20]Natsuaki M. Tick bites in Japan. J Dermatol 2021;48:423–30.

[21]Ando S, Fujita H. Diversity between spotted fever group rickettsia and ticks as vector. Eisei Dobutsu 2013;64:5–7.

[22]Thu MJ, Qiu Y, Matsuno K, Kajihara M, Mori-Kajihara A, Omori R, et al. Diversity of spotted fever group rickettsiae and their association with host ticks in Japan. Sci Rep 2019;9:1500.

[23]Tabara K, Kawabata H, Arai S, Itagaki A, Yamauchi T, Katayama T, et al. High incidence

298 of rickettsiosis correlated to prevalence of Rickettsia japonica among Haemaphysalis
299 longicornis tick. J Vet Med Sci 2011;73:507–10.
300 [24]Hofhuis A, Harms M, van den Wijngaard C, Sprong H, van Pelt W. Continuing increase of
301 tick bites and Lyme disease between 1994 and 2009. Ticks Tick Borne Dis 2015;6:69–74.
302 [25]Septfons A, Figoni J, Gautier A, Soullier N, de Valk H, Desenclos J-C. Increased
303 awareness and knowledge of Lyme Borreliosis and tick bite prevention among the general
304 population in France: 2016 and 2019 health barometer survey. BMC Public Health
305 2021;21:1808.
306 [26]Yang X, Gao Z, Wang L, Xiao L, Dong N, Wu H, et al. Projecting the potential distribution
307 of ticks in China under climate and land use change. Int J Parasitol 2021;51:749–59.
308 [27]Huang X, Li J, Li A, Wang S, Li D. Epidemiological Characteristics of Severe Fever with
309 Thrombocytopenia Syndrome from 2010 to 2019 in Mainland China. Int J Environ Res
310 Public Health 2021;18.
311 [28]Matsuyama H, Taira M, Suzuki M, Sando E. Associations between Japanese spotted fever
312 (JSF) cases and wildlife distribution on the Boso Peninsula, Central Japan (2006-2017). J
313 Vet Med Sci 2020;82:1666–70.
314 [29]Motoi Y, Asano M, Inokuma H, Ando S, Kawabata H, Takano A, et al. Detection of
315 Rickettsia tamurae DNA in ticks and wild boar (Sus scrofa leucomystax) skins in Shimane

316 Prefecture, Japan. J Vet Med Sci 2013;75:263–7.

317 [30]Ministry of the Environment. Available at: https://www.env.go.jp/press/109239.html.

318 Accessed October 10, 2024.

319 [31]Wilson N, Vahey GM, McDonald E, Fitzpatrick K, Lehman J, Clark S, et al. Tick bite risk

320 factors and prevention measures in an area with emerging Powassan virus disease. Public

321 Health Chall 2023;2.

322 [32]Piacentino JD, Schwartz BS. Occupational risk of Lyme disease: an epidemiological

323 review. Occup Environ Med 2002;59:75–84.

324 [33]Nadelman RB, Nowakowski J, Fish D, Falco RC, Freeman K, McKenna D, et al.

325 Prophylaxis with single-dose doxycycline for the prevention of Lyme disease after an Ixodes

326 scapularis tick bite. N Engl J Med 2001;345:79–84.

327 [34]Lantos PM, Rumbaugh J, Bockenstedt LK, Falck-Ytter YT, Aguero-Rosenfeld ME,

328 Auwaerter PG, et al. Clinical Practice Guidelines by the Infectious Diseases Society of

329 America (IDSA), American Academy of Neurology (AAN), and American College of

330 Rheumatology (ACR): 2020 Guidelines for the Prevention, Diagnosis, and Treatment of

331 Lyme Disease. Arthritis Care Res 2021;73:1–9.

332 [35]Gump DW, Ashikaga T, Fink TJ, Radin AM. Side effects of minocycline: different dosage

333 regimens. Antimicrob Agents Chemother 1977;12:642–6.

Figure Legend

Figure 1. Geographic location of the hotspot area of Japanese Spotted Fever (JSF)

Numakuma Hospital is located in southern Fukuyama City (Hiroshima Prefecture, Japan).

Figure 2. Annual incidence number of Japanese spotted fever reported in Japan and Hiroshima prefecture, (A) by year and (B) by week

Data for weekly distribution was the sum of those reported between 2016 and 2022.

Figure 3. Number of tick-bitten patients visiting the Japanese Spotted Fever hotspot hospital, (A) by year and (B) by month

Data for monthly distribution was the sum of reported between 2018 and 2023.

Figure 4. Distribution of tick bite sites

Of 305 cases, tick bite sites were identified in 178 (58%) cases.