Received: 12 March 2018 | Accepted: 18 May 2018
DOI: 10.1002/jmv.25239

RESEARCH ARTICLE

WILEY JOURNAL OF MEDICAL VIROLOGY

Fine-scale geographic clustering pattern of human T-cell leukemia virus type 1 infection among blood donors in Kyushu-Okinawa, Japan

Yasuko Sagara PhD[1] | Masako Iwanaga MD, PhD, MPH[2] | Maiko Morita MS[1] | Yasuhiro Sagara DSc[3] | Hitomi Nakamura MS[1] | Hideaki Hirayama BS[1] | Kazuo Irita MD, PhD[1]

[1]Department of Quality, Japanese Red Cross Kyushu Block Blood Center, Fukuoka, Japan
[2]Department of Frontier Life Science, Graduate School of Biomedical Sciences, Nagasaki University, Nagasaki, Japan
[3]Faculty of Education, Nakamura Gakuen University, Fukuoka, Japan

Correspondence
Yasuko Sagara, PhD, Department of Quality, Japanese Red Cross Kyushu Block Blood Center, 1-2-1 Kamikoga, Chikushino, Fukuoka 818-8588, Japan.
Email: y-sagara@qc.bbc.jrc.or.jp
Masako Iwanaga, MD, PhD, MPH, Department of Frontier Life Science, Nagasaki University Graduate School of Biomedical Sciences, 1-12-4 Sakamoto, Nagasaki 852-8523, Japan.
Email: masakoiwng@nagasaki-u.ac.jp

Funding information
Japanese Red Cross Blood Programme, Grant/Award Numbers: Grant Number 104 in Infectious Diseases, 104; Research Program on Emerging and Re-emerging Infectious Diseases of the Japan Agency for Medical Research and Development, AMED, Grant/Award Number: JP17fk0108110

Human T-cell leukemia virus type I (HTLV-1) infection is endemic in Japan, particularly clustered in the southwestern district, Kyushu-Okinawa, which consists of eight prefectures that further consist of 274 municipalities. However, no information is available about the fine-scale distribution of HTLV-1 infection within Kyushu-Okinawa. To assess the municipal-level distribution of people with HTLV-1 infection in Kyushu-Okinawa, we performed a cross-sectional study using a fine-scale geographic information system map based on HTLV-1 screening test results from the Japanese Red Cross database from September 2012 to February 2014. Of the 881 871 (646 914 male, 234 957 female) screened blood donors, 981 were seropositive for HTLV-1 by confirmatory test. The seroprevalence was 0.11% (95% confidence interval [CI] 0.10%-0.12%) for all, 0.094% (95% CI, 0.09%-0.10%) for male, and 0.16% (95% CI, 0.14%-0.18%) for female individuals. The sex- and age-specific HTLV-1 seroprevalence varied significantly across municipalities; particularly, the seroprevalence among women aged 50 years was significantly higher than that of men in both the mainland of Kyushu-Okinawa and the satellite island, in all of which the seroprevalence of HTLV-1 was more than 1.2%. These results show that, even in the Kyushu-Okinawa district, there are endemic clusters of HTLV-1 in small areas. This suggests that public health education programs are needed to eliminate new HTLV-1 infection in these areas.

KEYWORDS
blood donors, fine-scale distribution, human T-cell leukemia virus type I (HTLV-1), Japan, seroprevalence

1 | INTRODUCTION

Human T-cell leukemia virus type I (HTLV-1) is the causative agent of adult T-cell leukemia/lymphoma,[1,2] HTLV-1-associated myelopathy/tropical spastic paraparesis,[3] and various systemic inflammatory diseases.[4] People infected with HTLV-1 are distributed worldwide, with an

Abbreviations: CLEIA, chemiluminescent enzyme immunoassay; HAM/TSP, HTLV-1-associated myelopathy/tropical spastic paraparesis; HTLV-1, human T-cell leukemia virus type I; JRC, Japanese Red Cross; 95% CIs, 95% confidence intervals.

estimated 20 million infected, but endemic areas are limited to Japan, Brazil, West and Central Africa, the Caribbean islands, and other small areas.[5,6] HTLV-1 transmission occurs via breast milk, blood transfusion, needle sharing, solid-organ transplantation, and possibly sexual contact with a partner with HTLV infection.[5-9] In Japan, transfusion-transmission of HTLV-1 has been almost eliminated since blood-donor screening for HTLV-1 infection was implemented in 1986 by the Japanese Red Cross (JRC).[10] Mother-to-child transmission in HTLV-1-endemic areas has been also declining since HTLV-1 screening for pregnant women become widespread.[11] Nevertheless, it is estimated that approximately one million people are infected with HTLV-1,[12] and approximately 4000 new people are infected with HTLV-1 annually in Japan.[13]

Even in countries where HTLV-1 is endemic, there is further regional distribution disparity. In Brazil, HTLV-1-infected mothers are clustered in the northeastern and metropolitan areas, but the rate is low in the southern region.[14] In the Caribbean islands, HTLV-1 seroprevalence is high in Jamaica and the French West Indies, but not in Cuba.[6] In Japan, blood donors infected with HTLV-1 are clustered in the southwestern area.[12,15] However, most of the prior Japanese studies on HTLV-1 seroprevalence were based only on a unit of seven large regions (Hokkaido, Tohoku, Kanto, Hokuriku-Chubu, Kinki, Chugoku-Shikoku, and Kyushu-Okinawa) or a unit of 47 prefectural-level regions; none of those studies showed the fine-scale geographic variation of HTLV-1-seroprevalence within each region. For the development of effective prevention strategies to eliminate new HTLV-1 infection, it is important to determine whether HTLV-1 infection is distributed evenly within each region or is clustered in some areas, particularly the Kyushu-Okinawa region, which is known as one of the most endemic areas for HTLV-1 in the world. However, so far, no studies have reported such a detailed geographical distribution of HTLV-1 infection in the HTLV-1-endemic region in Japan.

Therefore, the aim of this study was to assess the fine-scale distribution of people infected with HTLV-1 in the most HTLV-1-endemic region, Kyushu-Okinawa, based on HTLV-1 confirmatory test results of blood donors.

2 | MATERIAL AND METHODS

2.1 | Study design

We performed a cross-sectional analysis to assess HTLV-1 seroprevalence at the municipal level in Kyushu-Okinawa, based on serological HTLV-1 confirmatory test results of donated blood samples in the database of the JRC Kyushu Block Blood Center, Fukuoka, Japan.

2.2 | Study area and demographic data sources

Japan has three levels of government: national, prefectural, and municipal. Thus, it consists of 47 prefectures, each of which consists of numerous "municipalities" (more than 1500) named as city, town, village, or ku. In the current study, we focused on the southwestern area of Japan, which is named the Kyushu-Okinawa area (Figure 1A). It consists of eight prefectures: Fukuoka, Saga, Nagasaki, Kumamoto, Oita, Miyazaki, Kagoshima, and Okinawa (Figure 1B). The eight prefectures are further divided into 274 municipalities, including islands (Table 1 and Figure 1C). The population in each of the eight

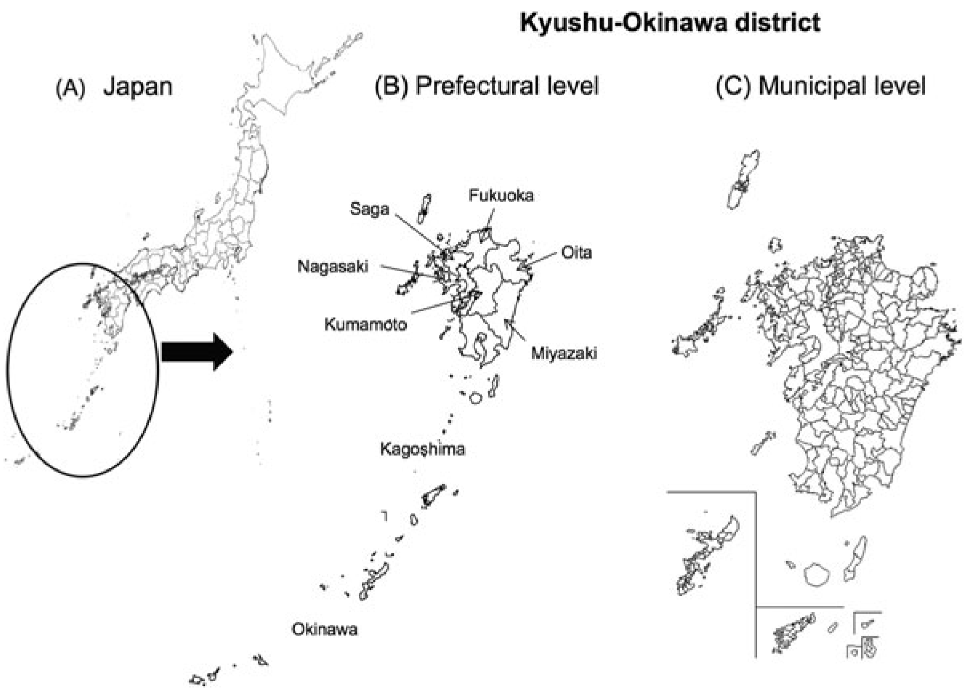

FIGURE 1 Maps of Japan and the Kyushu-Okinawa district. (A) Japan. (B) Locations of eight prefectures. (C) Fine-scale sections of municipalities in each prefecture. Maps were obtained from the Geospatial Information Authority of Japan (http://www.gsi.go.jp/index.html), Teikoku-Shoin Co, Ltd, Japan (https://www.teikokushoin.co.jp), and the MANDARA software package[16]

TABLE 1 Summary of prefectural-level administrative and demographic data of the Kyushu-Okinawa area

Name of prefecture	Total population	Male population	Female population	No. municipalities	No. islands
Fukuoka	5 085 000	2 400 000	2 686 000	60	62
Saga	843 000	397 000	446 000	20	55
Nagasaki	1 408 000	657 000	750 000	21	971
Kumamoto	1 807 000	849 000	958 000	45	178
Oita	1 185 000	560 000	625 000	18	109
Miyazaki	1 126 000	529 000	597 000	26	179
Kagoshima	1 690 000	790 000	900 000	43	605
Okinawa	1 409 000	691 000	718 000	41	363
Total	**14 553 000**	**6 873 000**	**7 680 000**	**274**	**2522**

The 2013 population data were obtained from the Statistics Bureau, Ministry of Informal Affairs and Communications of Japan (http://www.stat.go.jp/data/jinsui/2013np/). The 2013 municipalities' data were obtained from the Ministry of Internal Affairs and Communications of Japan (http://www.soumu.go.jp/kouiki/kouiki.html). The 2013 islands data were obtained from the Japan Oceanographic Data Center (http://www.jodc.go.jp/).

prefectures in 2013 (the midpoint year of the study period) is summarized by age and sex in Table 1. The 2013 demographic data from each of the 274 municipalities were obtained by the Ministry of Internal Affairs and Communications of Japan and the Statistics Bureau. The number of islands in 2013 were obtained by the Japan Oceanographic Data Center.

2.3 | HTLV-1 serological testing system of the JRC

All the donated blood samples were routinely screened for HTLV-1 using a CLEIA (CL4800 Testing System, Fujirebio, Japan) according to the manufacturer's instructions. The assay uses coated microparticles with an antigen purified from HTLV-1-infected cell lysate, a culture supernatant, and a chemiluminescent readout. Reactive samples that showed more than the cutoff value underwent further testing for confirmation. All of the CLEIA test-positive samples were confirmed by Western blot analysis (Problot HTLV-I; Fujirebio, Japan) as a confirmatory test. The decision about reactivity was made according to manufacturer's protocol. In the case of both the *Gag* and *Env* bands being visible with greater intensity than the weak positive control, the specimen was considered "seropositive," but if only the *Gag* or *Env* band was observed, the specimen was considered "deferred." If no bands were present, the sample was considered "seronegative."

2.4 | Data extraction of HTLV-1 serological test results

This study was approved by the ethics committee of the JRC (No. 2014-014). No written informed consent was required because of the nature of the study design, which was based on a retrospective review of individually anonymized blood test results from the JRC Blood Service Headquarters database. In January 2015, we extracted HTLV-1 confirmatory test results from 2012 to 2014, including sex, age at donation, and postal code of address (to determine prefecture and municipal area of residence). For data from repeated donors, we only included the results of the first donation during the study period.

The extracted data from the HTLV-1 serological test results were then grouped by sex, age, and municipal level based on postal code to calculate the age- and sex-specific HTLV-1 seroprevalence among blood donors at each municipal level.

2.5 | Geographic distribution map

To visualize the age- and sex-specific seroprevalence of HTLV-1 (%) at the municipal level, we used a free Geographic Information System software package, MANDARA (version 9.45, Japan) (http://ktgis.net/mandara/).[16] MANDARA has been used in several geographic distribution studies.[17-19]

2.6 | Statistical analysis

We computed the seroprevalence of HTLV-1 (%) by dividing the numbers of confirmed HTLV-1-positive donors by the total numbers of screened donors during 2012-2014 by age category, sex, prefectural level, and municipal level. Continuous data were summarized as median and interquartile range and compared by group using the Wilcoxon rank sum test. The group-wise comparison of HTLV-1 seroprevalence used a log-binomial regression model and estimated the seroprevalence ratios with 95% confidence intervals (95% CIs). All statistical analyses were performed using the SAS software package (version 9.4, SAS Institute, Cary, NC) and JMP Pro13 software (SAS Institute) with the two-tailed alpha level set to 0.05.

3 | RESULTS

3.1 | HTLV-1 seroprevalence among blood donors throughout Kyushu-Okinawa

During 2012-2014, a total of 884 438 blood donors (649 017 male and 235 421 female) received HTLV-1 screening tests throughout

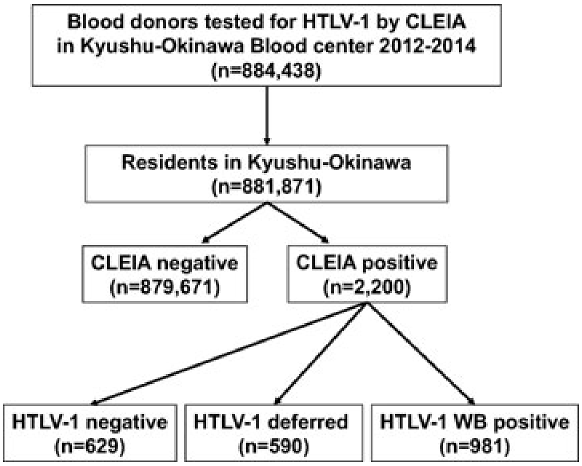

FIGURE 2 Flow chart of HTLV-1 screening procedure and conformation of HTLV-1 positive blood donors in the Japanese Red Cross Kyushu Block Blood Center. CLEIA, chemiluminescent enzyme immunoassay; HTLV-1, human T-cell leukemia virus type I; WB, Western blot

the entire Kyushu-Okinawa district; of those, 881 871 (646 914 male and 234 957 female) were residents of Kyushu-Okinawa according to their postal code information (Figure 2). Therefore, we considered those 881 871 donors as our study population. The age distribution of the study population is summarized in Table 2, with the most frequent age group being 40-49 years. Among the 881 871 blood donors, a total of 2200 (1439 male and 761 female) were seropositive for HTLV-1 by CLEIA screening test. Among those with positive CLEIA results, 981 (44.6%) had positive Western blot tests (Figure 2); of those, 605 were male and 376 were female (Table 2). The positive rate of HTLV-1 among blood donors with Kyushu-Okinawa postal codes was 0.11% (95% CI, 0.10%-0.12%) for all donors and 0.094% and 0.16% for male and female donors, respectively (Table 2). The female/male ratio was 1.71 (95% CI, 1.50-1.95), indicating that the HTLV-1 positive rate was significantly higher in female than male donors ($P < 0.0001$). The ages of the HTLV-1-positive blood donors ranged from 16 to 65 years with a median of 48 years (interquartile range 35-56 years) for male donors and from 16 to 68 years with a median of 53 years (interquartile range 43-58) for female donors. Among the HTLV-1-positive blood donors, the most frequent age group was 50-59 years (Table 2 and Figure 3A).

3.2 | Difference in HTLV-1 seroprevalence at prefectural level

Although the Kyushu-Okinawa area is known to be the region in which HTLV-1 is most endemic in Japan, the HTLV-1-serpositive rate differs by prefectural level throughout the area (Table 2 and Figure 3B). Overall, the seropositive rate was relatively low in the northern and eastern parts of Kyushu (Fukuoka, Saga, and Oita), whereas it was high in the western and southern parts of Kyushu (Nagasaki, Kumamoto, Miyazaki, Kagoshima,

TABLE 2 Summary of HTLV-1 seropositivity in blood donors by gender, age, and prefecture

	Total		Male		Female			
	No.	HTLV-1 positive, (% of row)	No.	HTLV-1 positive, (% of row)	No.	HTLV-1 positive, (% of row)	Female/male rate ratio (95%CI)	*P* value
No. (%)	881 871	981 (0.11)	646 914	605 (0.094)	234 957	376 (0.16)	1.71 (1.50-1.95)	<0.0001
Age, y								
16-19	49 023	48 (0.098)	34 020	34 (0.100)	15 003	14 (0.093)	0.93 (0.50-1.73)	0.820
20-29	156 001	99 (0.063)	105 155	78 (0.074)	50 846	21 (0.041)	0.56 (0.34-0.90)	0.017
30-39	204 679	124 (0.061)	150 758	92 (0.061)	53 921	32 (0.059)	0.97 (0.65-1.45)	0.890
40-49	237 434	209 (0.088)	180 502	133 (0.074)	56 932	76 (0.133)	1.81 (1.37-2.40)	<0.001
50-59	169 225	360 (0.213)	128 000	193 (0.151)	41 225	167 (0.405)	2.68 (2.18-3.30)	<0.001
60-69	65 509	141 (0.215)	48 479	75 (0.155)	17 030	66 (0.388)	2.51 (1.80-3.49)	<0.001
Prefecture								
Fukuoka	300 389	212 (0.071)	212 530	125 (0.059)	87 859	87 (0.099)	1.68 (1.28-2.21)	<0.001
Saga	49 753	39 (0.078)	36 019	25 (0.069)	13 734	14 (0.102)	1.47 (0.76-2.83)	0.281
Nagasaki	89 845	119 (0.132)	69 179	66 (0.095)	20 666	53 (0.256)	2.69 (1.87-3.86)	<0.001
Kumamoto	116 269	87 (0.075)	85 168	49 (0.058)	31 101	38 (0.122)	2.12 (1.39-3.24)	<0.001
Oita	74 112	61 (0.082)	54 062	37 (0.068)	20 050	24 (0.120)	1.75 (1.05-2.92)	0.033
Miyazaki	76 899	104 (0.135)	57 051	64 (0.112)	19 848	40 (0.202)	1.80 (1.21-2.67)	0.004
Kagoshima	102 545	202 (0.197)	75 421	131 (0.174)	27 124	71 (0.262)	1.51 (1.13-2.01)	0.005
Okinawa	86 151	157 (0.182)	68 340	108 (0.158)	17 811	49 (0.275)	1.74 (1.24-2.44)	0.001

HTLV-1, human T-cell leukemia virus type I.

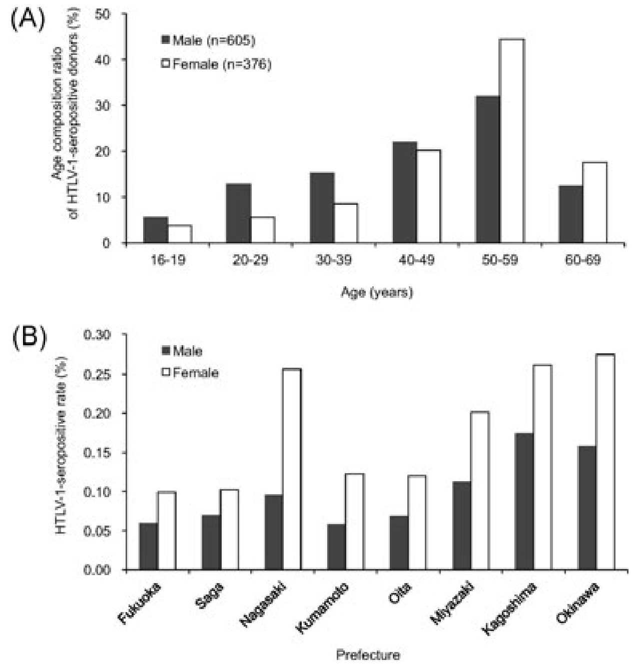

FIGURE 3 Rates of HTLV-1-seropositive blood donors by demographic information throughout the entire Kyushu-Okinawa area. (A) By sex and age group. The *Y* axis indicates the age composition ratio of HTLV-1-seropositive donors (%). (B) By sex and prefecture. The *Y* axis indicates the HTLV-1-seropositive rate (%). HTLV-1, human T-cell leukemia virus type I

and Okinawa). Furthermore, in all prefectures except Saga Prefecture, HTLV-1 seropositivity was significantly higher in female than male donors, particularly in Nagasaki Prefecture (female-to-male ratio: 2.69). When we analyzed the relationship between HTLV-1 positive rate and the number of island per population at prefectural level using a simple linear correlation analysis, overall there were positive linear correlations between the two factors (Supporting Information Figure S1A-C); in particular, in female (Supporting Information Figure S1C), the relationship was statistically significant ($P = 0.023$).

3.3 | Difference in HTLV-1 seroprevalence at municipal level

Additional fine-scale mappings of 274 municipal-level divisions with age- and sex-specific HTLV-1-serpositivity are shown in Figure 4. In the younger group (Figure 4A,B show the patterns of aged 16-19 and 20-29 years, respectively), rates more than 1.2% of HTLV-1-seropositivity was scattered throughout limited rural depopulated areas, such as mountainous regions; however, in older adults (Figure 4E,F: aged 50-59 years and 60-69 years, respectively), relatively high rates of HTLV-1-seropositivity were distributed widely throughout qKyushu-Okinawa, particularly in female aged 50-59 years in island areas. When we analyzed a simple relationship between HTLV-1 positive rate and the population density of residential area at municipal level using a simple linear correlation, overall there were weak-negative linear correlations between the two factors (Supporting Information Figure S1D-F); in particularly in male (Supporting Information Figure S1E), the relationship was marginally statistically significant ($P = 0.077$).

4 | DISCUSSION

In this study, for the first time, we provided fine-scale (municipal level) epidemiological evidence of HTLV-1 seroprevalence in the Kyushu-Okinawa district in Japan, one of the areas of the world where HTLV-1 is most endemic. Our main findings are the following: (a) HTLV-1-seropositive people are distributed unevenly by sex and by age group even at the municipal level; (b) the seroprevalence of female aged 50-59 years was significantly higher than that of male in all fine-scale regions, including islands, coastal areas, and mountainous regions; and (c) high rates of younger HTLV-1-seropositive individuals were scattered across narrow municipal areas.

In the 1980s, several serological surveys for antibody to HTLV-1 were conducted throughout Japan and have suggested that HTLV-1-seropositivity may be high in rural islands or coastal regions.[15,20,21] However, the earlier studies included only a few selected rural areas. Therefore, the results of the current study add new information on the current epidemiological features of HTLV-1 infection at broad- and fine-scale areas in the Kyushu-Okinawa district. We confirmed that, even in the modern era, HTLV-1-seropositive people are still distributed unevenly by sex and by age group; particularly, highly endemic areas were scattered throughout depopulated areas, such as islands and mountainous regions.

Recently, the fine-scale distributions of blood donors infected with HTLV-1 have been reported from several countries using Geographic Information System software. San Martín et al[22] reported 706 (1.02%) HTLV-1/2 positive cases among 694 016 Chilean blood donors from 2011 to 2013 and found that the HTLV-1 prevalence rates differed across 15 regions. They suggested that the regional difference in seroprevalence may be affected by immigrant or descendant history. Chang et al[23] has also reported a fine-scale distribution map of 104 HTLV-1 positive blood donors among 2 047 740 first-time donors in a large network of US blood centers, suggesting that the high-prevalence spot area was associated with immigration from HTLV-1 hyperendemic areas, such as Japan, the Caribbean, and sub-Saharan African countries. In these countries together, not only "immigrant or descendant history from HTLV-1-endemic areas" but also "lower socioeconomic status," "low educational attainment," and "race/ethnicity" may affect the scattered high-prevalence areas; these explanations might be reasonable based on their histories.

However, none of the above background factors are applicable to Japan because of its small ethnic diversity, high educational standards, few immigrants, and very rare occurrence of zoonotic infection.[24] Therefore, the reason why people with HTLV-1 infection are clustered in small, remote regions in the Kyushu-Okinawa area is still unknown.[25] The only possible speculation is that there is less exchange between people living in rural regions or islands and those in urban regions. This speculation may be plausible based on results of the current study; first, because Nagasaki, Kagoshima, and Okinawa prefectures are the best

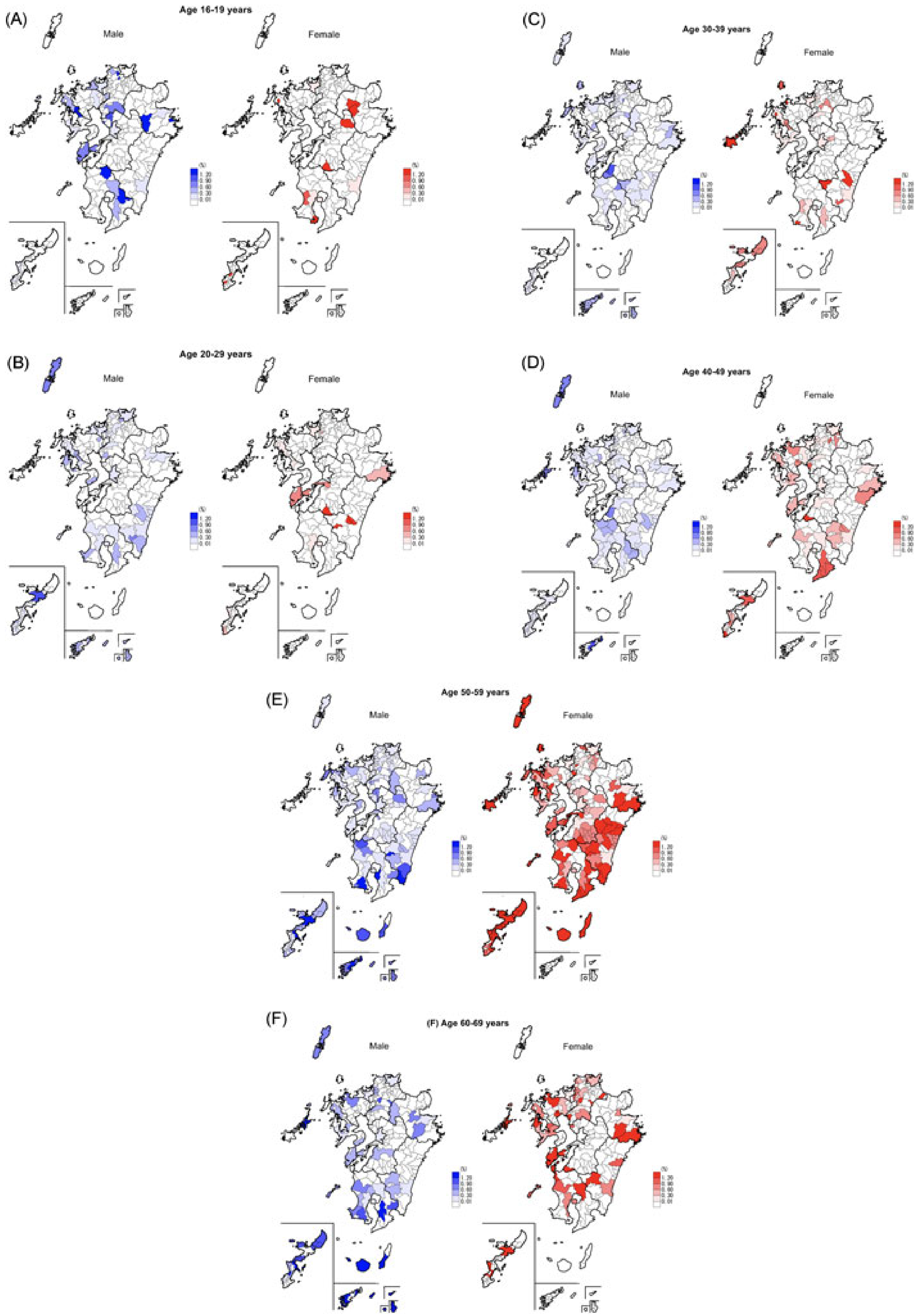

FIGURE 4 Geographical distribution of sex- and age-specific HTLV-1-seroprevalence among blood donors at the municipal level in Kyushu-Okinawa. Each color gradation represents HTLV-1-seroprevalence (%) among blood donors in each municipality. The figures on the left (blue) for each age-group panel show the results for male donors and those on the right (red) for female donors, respectively. (A) Age 16-19 years. (B) Age 20-29 years. (C) Age 30-39 years. (D) Age 40-49 years. (E) Age 50-59 years. (F) Age 60-69 years. HTLV-1, human T-cell leukemia virus type I

three in terms of the number of islands (Table 1), second, because the three prefectures are the best three in terms of the highest rates of HTLV-1 seropositivity in female donors (Table 2 and Figure 3B) with a positive linear correlation between HTLV-1 positive rate and the number of island per population in female (Supporting Information Figure S1C), and finally, because there was a weak-negative linear correlation between HTLV-1 positive rate and the population density (Supporting Information Figure S1D-F). The different distributions of high HTLV-1 seroprevalence in those aged 16-19 years and 20-29 years in some small, remote regions (Figure 4A,B) may be also explained by differences in exchange between people: in Japan, people aged younger than 20 years are regarded as "underage," and parents are legally obliged to protect and supervise their children aged under 20 years.

As for age distribution, in the current study, HTLV-1 seroprevalence in donors aged 16-19 and 20-29 years were lower than those in older generations. In Japan, this may be caused by the natural decrease of HTLV-1 infection due to the effects of the HTLV-1 screening program for pregnant women[11] and the shortening of the breastfeeding period in Japan in recent decades. However, recent studies in the United States[23] and Iran[26] also showed a natural decline of HTLV-1 seroprevalence in each country. These natural declines can be explained by a birth-cohort effect.[27] However, in the current study, high HTLV-1 prevalence was observed even in the adolescent generation in limited municipalities nearby mountainous and island regions (Figure 4A). Social factors specific to the lifestyle in these remote regions, such as long breastfeeding duration, might influence the spread of HTLV-1 infection. Furthermore, we recently revealed that new HTLV-1 infection occurs more frequently in people in their 40s and 50s than in younger generations in Japan.[13] Such new HTLV-1 infection may partially contribute to the increased seroprevalence in older adults.

The strength of this study lies in the large sample size and the first-time comprehensive assessment of people with HTLV-1 infection at the municipal level of Kyushu-Okinawa, the region where HTLV-1 is most endemic. One new finding is that people infected with the virus are unevenly scattered in small, remote areas even within Kyushu-Okinawa. Nevertheless, the current study has several limitations. First, the use of HTLV-1 test results from blood donors might be affected by selection bias due to the so-called healthy donor effect because blood donors need to pass specific health and lifestyle criteria before donating blood.[28] Second, the male-female ratio significantly differed between the general population of Kyushu-Okinawa (approximately 0.9) and blood donors (approximately 2.8), which also might affect this study's results. Using blood donors to represent the general population has been debated everywhere.[29] Therefore, the male-female difference in HTLV-1 seroprevalence in the current study might be an underestimation or overestimation of the true difference. Third, although the current study analyzed the geographical distribution of seroprevalence at the fine-scale administrative district level, we did not consider latitude, longitude, and altitude. Therefore, we did not clearly define "small, remote areas," such as mountainous areas. This suggests that more detailed analyses are warranted.

Since the discovery in the 1980s that Japan is the area in which HTLV-1 is most endemic, the rates of HTLV-1-infected people have remained high. However, so far there has been little effort to reduce infection in Japan. Furthermore, around 10-20 million people are infected worldwide. In response to this global burden of HTLV-1 infection, an international research group called "the Global Virus Network" launched a taskforce to develop new methods of prevention and treatment of HTLV-1 infection in 2014.[30] To reduce HTLV-1 infection in Japan, it is necessary to develop more effective measures and educational programs to inform all age groups about infection routes of HTLV-1 other than breast milk.[31] We hope that further investigations will clarify the mechanisms of infection and develop preventive systems against the spread of HTLV-1 in Japan.

ACKNOWLEDGMENTS

We thank all the blood donors and staff at the Japanese Red Cross Kyushu Block Blood Center. This study was supported in part by the Japanese Red Cross Blood Programme (Grant number 104 in Infectious Diseases) for Y Sagara and in part by the Research Program on Emerging and Re-emerging Infectious Diseases of the Japan Agency for Medical Research and Development, AMED (JP17fk0108110) for Y Sagara and M Iwanaga . We thank Richard Lipkin, PhD, from Edanz Group (www.edanzediting.com/ac) for editing a draft of this manuscript.

CONFLICTS OF INTEREST

All authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

AUTHORS' CONTRIBUTIONS

Design of research: YS, MI, MM, and YHS. Data acquisition: YS, MM, HN, HH, and KI. Data analysis: YS, MI, and MM. Data interpretation and drafting of the manuscript: YS, MI, and MM. Critical review of the draft: YHS, HN, HH, and KI. Revision of initial draft and writing of final draft: YS and MI. All authors reviewed and approved the final version of the manuscript.

ORCID

Masako Iwanaga http://orcid.org/0000-0003-1148-6192

REFERENCES

1. Yoshida M, Miyoshi I, Hinuma Y. Isolation and characterization of retrovirus from cell lines of human adult T-cell leukemia and its implication in the disease. *Proc Natl Acad Sci USA*. 1982;79: 2031-2035.
2. Poiesz BJ, Ruscetti FW, Gazdar AF, Bunn PA, Minna JD, Gallo RC. Detection and isolation of type C retrovirus particles from fresh and

cultured lymphocytes of a patient with cutaneous T-cell lymphoma. *Proc Natl Acad Sci USA*. 1980;77:7415-7419.
3. Osame M, Usuku K, Izumo S, et al. HTLV-I associated myelopathy, a new clinical entity. *Lancet*. 1986;3:1031-1032.
4. Goncalves DU, Proietti FA, Ribas JGR, et al. Epidemiology, treatment, and prevention of human T-cell leukemia virus type 1-associated diseases. *Clin Microbiol Rev*. 2010;23:577-589.
5. Proietti FA, Carneiro-Proietti ABF, Catalan-Soares BC, Murphy EL. Global epidemiology of HTLV-1 infection and associated diseases. *Oncogene*. 2005;2:6058-6068.
6. Gessain A, Cassar O. Epidemiological aspects and world distribution of HTLV-1 infection. *Front Microbiol*. 2012;3:388.
7. Feigal E, Murphy E, Vranizan K, et al. Human T cell lymphotropic virus types I and II in intravenous drug users in San Francisco: risk factors associated with seropositivity. *J Infect Dis*. 1991;164:36-42.
8. Waggoner JJ, Soda EA, Deresinski S. Rare and emerging viral infections in transplant recipients. *Clin Infect Dis*. 2013;57:1182-1188.
9. Toro C, Rodes B, Poveda E, Soriano V. Rapid development of subacute myelopathy in three organ transplant recipients after transmission of human T-cell lymphotropic virus type I from a single donor. *Transplantation*. 2003;75:102-104.
10. Inaba S, Sato H, Okochi K, et al. Prevention of transmission of human T-lymphotropic virus type 1 (HTLV-1) through transfusion, by donor screening with antibody to the virus. One-year experience. *Transfusion*. 1989;29:7-11.
11. Miura K, Masuzaki H. Prevention of human T-cell leukemia virus type 1 (HTLV-1) mother-to-child transmission. *Adult T-cell Leukemia/Lymphoma*. Japan: Springer; 2017:157-169.
12. Satake M, Yamaguchi K, Tadokoro K. Current prevalence of HTLV-1 in Japan as determined by screening of blood donors. *J Med Virol*. 2012;84:327-335.
13. Satake M, Iwanaga M, Sagara Y, Watanabe T, Okuma K, Hamaguchi I. Incidence of human T-lymphotropic virus 1 infection in adolescent and adult blood donors in Japan: a nationwide retrospective cohort analysis. *Lancet Infect Dis*. 2016;16:1246-1254.
14. Ribeiro MA, Proietti FA, Martins ML, et al. Geographic distribution of human T-lymphotropic virus types 1 and 2 among mothers of newborns tested during neonatal screening, Minas Gerais, Brazil. *Rev Panam Salud Publica*. 2010;27:330-337.
15. Maeda Y, Furukawa M, Takehara Y, et al. Prevalence of possible adult t-cell leukemia virus-carriers among volunteer blood donors in Japan: a nation-wide study. *Int J Cancer*. 1984;33:717-720.
16. Tani K, Sato T, Ohnishi K, Okamoto K, Okunuki K. Development of an educational GIS and its use on a trial basis in junior high school classes. *Theory Appl GIS*. 2002;10:69-77.
17. Luo, P, He B, et al. Spatiotemporal trend analysis of recent river water quality conditions in Japan. *J Environ Monit*. 2011;13:2819-2829.
18. Horiuchi S, Morino M. How local cultures contribute to local communities? Case studies of Japanese spirits dance 'Kagura'*IJSSH*. 2015;5:58-62.
19. Nguyen BM, Arakawa E, Izumiya H, et al. Molecular epidemiology of *Vibrio cholerae* O1 in northern Vietnam (2007-2009), using multilocus variable-number tandem repeat analysis. *J Med Microbiol*. 2016;65:1007-1012.
20. Hinuma Y, Komoda H, Chosa T, et al. Antibodies to adult t-cell leukemia-virus-associated antigen (ATLA) in sera from patients with ATL and controls in japan: a nationwide sero-epidemiologic study. *Int J Cancer*. 1982;29:631-635.
21. Kohakura M, Nakada K, Yonahara M, Komoda H, Imai J, Hinuma Y. Seroepidemiology of the human retrovirus (HTLV/ATLV) in Okinawa where adult T-cell leukemia is highly endemic. *Jpn J Cancer Res*. 1986;77:21-23.
22. San Martín H, Balanda M, Vergara N, et al. Human T-lymphotropic virus type 1 and 2 seroprevalence among first-time blood donors in Chile, 2011-2013. *J Med Virol*. 2016;88:1067-1075.
23. Chang YBZ, Hindes D, et al. Seroprevalence and demographic determinants of human T-lymphotropic virus type 1 and 2 infections among first-time blood donors-United States, 2000-2009. *J Infect Dis*. 2014;209:523-531.
24. Filippone C, Betsem E, Tortevoye P, et al. A severe bite from a nonhuman primate is a major risk factor for HTLV-1 infection in hunters from central africa. *Clin Infect Dis*. 2015;60:1667-1676.
25. Sonoda S, Li HC, Tajima K. Ethnoepidemiology of HTLV-1 related diseases: ethnic determinants of HTLV-1 susceptibility and its worldwide dispersal. *Cancer Sci*. 2011;102:295-301.
26. Karimi G, Zadsar M, Pourfathollah AA. Seroprevalence and geographical distribution of human T-lymphotropic virus type 1 among volunteer blood donors in endemic areas in Iran. *Virology J*. 2017;14:14.
27. Ueda K. Cohort effect on HTLV-I seropoprevalence in southern Japan. *Lancet*. 1989;2:979.
28. Atsma F, Veldhuizen I, Verbeek A W, de Vegt F. Healthy donor effect: its magnitude in health research among blood donors. *Transfusion*. 2011;51:1820-1828.
29. Karaosmanoglu HK, Aydin OA, Sandikci S, Yamanlar ER, Nazlican O. Seroprevalence of hepatitis B: do blood donors represent the general population? *J Infect Dev Ctries*. 2012;6:181-183.
30. Willems L, Hasegawa H, Accolla R, et al. Reducing the global burden of HTLV-1 infection: an agenda for research and action. *Antiviral Res*. 2017;137:41-48.
31. Watanabe T. Current status of HTLV-1 infection. *Int J Hematol*. 2011;94:430-434.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

How to cite this article: Sagara Y, Iwanaga M, Morita M, et al. Fine-scale geographic clustering pattern of human T-cell leukemia virus type 1 infection among blood donors in Kyushu-Okinawa, Japan. *J Med Virol*. 2018;90:1658-1665. https://doi.org/10.1002/jmv.25239