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Early-onset and late-onset group B streptococcal disease in Japan: a nationwide surveillance study, 2004–2010

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SUMMARY

Objectives: To clarify the incidence and prognosis of early-onset (EOD) and late-onset (LOD) GBS disease in Japan. To evaluate the influence of national guidelines issued in 2008 on the epidemiology of GBS disease.
Methods: Retrospective nationwide questionnaire surveillance on culture-confirmed GBS infections between 2004 and 2010.
Results: Eighty-eight EOD and 162 LOD cases were reported from 152 participating hospitals. The case fatality of EOD was 13.6% and of LOD was 8.0%. Premature birth <37 weeks ($p < 0.001$) and low birth weight <2500 g ($p < 0.001$) were significantly associated with EOD mortality. A high rate of neurological sequelae was noted in meningitis in EOD (8/24) and LOD (29/85) cases. Based on a live-birth number of 438 359 and inborn case numbers of 36 EOD and 42 LOD, the incidence of EOD and LOD were estimated to be 0.08 (95% confidence interval (CI) 0.06–0.11)/1000 and 0.10 (95% CI 0.07–0.12)/1000 live-births, respectively. Before (2004–2008) and after (2009–2010) the issue of guidelines, the mortality of EOD (from 14.8% to 11.8%) and LOD (from 9.8% to 2.5%) improved, but the incidence was unchanged.
Conclusions: The incidence of EOD and LOD is apparently low in Japan, but the mortality and morbidity rates remain substantial. The issue of national guidelines did not affect the incidence.

1. Introduction

Group B Streptococcus (GBS, *Streptococcus agalactiae*) is a leading cause of invasive infections such as sepsis and meningitis in infants aged younger than 3 months. The infections are classified as early-onset disease (EOD) at age 0–6 days, and as late-onset disease (LOD) at age 7–89 days. Guidelines from the Centers for Disease Control and Prevention (CDC) for the prevention of EOD were issued in the USA in 1996, and updated in 2002 and 2010.[1–3] Implementation in the USA and other high-income countries has led to a significant decline in the incidence of EOD, but has had no effect on the incidence of LOD.[4–6]

In Japan, national guidelines to prevent vertical GBS transmission were issued in 2008 and revised in 2011.[7] The Japanese revised guidelines recommend cultures from the vagina, perineum, and rectum in all pregnant women at 33–37 weeks of gestation. The use of intrapartum antimicrobial prophylaxis (IAP) is indicated for (1) women whose previous infant had GBS disease, (2) women with a positive GBS culture, except those undergoing an elective cesarean section, and (3) women with an unknown GBS status at delivery irrespective of gestational week; however, these Japanese guidelines are not based on the epidemiology of neonatal GBS infections in Japan, but rather on that of the USA.

A recent systematic review indicated that the global burden of GBS disease is still high in both EOD and LOD, with substantial mortality and morbidity.[4,5] The review also showed considerable geographic differences in the incidence and prognosis;[4,5] however limited data on neonatal GBS infections are available for Asian countries,[4,8,9] and most have been derived from a single-center study.[8] In Japan, the first to fourth nationwide surveillances were conducted between 1983 and 2003; however, these reports had several problems when compared with data from other countries.[6,8–14] First, they analyzed patients without discriminating culture-confirmed cases from probable cases not proven by culture. Second, they were not written in English, although some parts of the first three studies were later published in English.[15] Third, in Japan, 48–49% of newborns are born in private clinics without pediatricians and/or neonatologists,[16] and newborns with EOD occurring under these circumstances must be transferred. Thus, the birth place is a worthwhile subject, but the prognosis with regard to the different birth places has not been addressed. Finally, the incidence of EOD and LOD has not been assessed.

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We conducted the fifth nationwide multicenter surveillance on EOD and LOD between 2004 and 2010. Our aim was to answer the aforementioned unresolved concerns and to evaluate if the national guidelines have influenced the clinical presentation and incidence of neonatal GBS disease.

2. Methods

2.1. Study setting and design

A retrospective questionnaire surveillance was conducted from January 1, 2004 to December 31, 2010. We mailed structured survey forms to 498 hospitals where education programs authorized by the Ministry of Health, Labor and Welfare have been adopted for postgraduate clinical training. Information was obtained based on the discharge register of each hospital. The study was approved by the Ethics Committee of Sanno Hospital, Tokyo; informed consent was not required.

2.2. Data collection and case definition

Data collection included (1) number of deliveries and live-births, (2) number of maternal transfers and neonatal transfers, (3) implementation (or not) of GBS prevention practices from either the CDC or Japanese guidelines, and the time if implemented, (4) infantile and maternal demographic features, (5) initial symptoms, diagnosis, and bacteria isolation site of EOD and LOD cases, (6) case fatality and neurological sequelae that were determined at hospital discharge by chart review, and (7) culture screening for mothers whose babies had EOD and LOD. Four obstetric risk factors were also documented: preterm birth, premature rupture of membranes for >18 h, intrapartum fever (>38 °C), and previous sibling with GBS disease.

Preterm birth was defined as <37 weeks of gestation; the number of days of gestation was not collected. We defined invasive GBS disease as laboratory isolation of *S. agalactiae* from a normally sterile site (blood, cerebrospinal fluid (CSF), or joint aspirate) with any clinical signs. Pneumonia is a respiratory distress syndrome with a radiological appearance of streaky opacity or confluent lobar opacification that commonly requires mechanical ventilation in addition to a positive blood culture result.

2.3. Microbiology

GBS serotyping was determined using a commercially available kit (Denka Seiken, Tokyo).

2.4. Estimation of the incidence of EOD and LOD

To estimate the institution-based incidence, we first counted the number of EOD and LOD infants who were born from mothers obstetrically managed throughout pregnancy at the relevant hospital (inborn cases). We excluded from the calculation those GBS cases whose mothers were transferred from another hospital within approximately 2 weeks before delivery (maternal transfer cases) and GBS cases that were born outside and transferred after the onset of the disease (outborn cases). Second, we collected the number of live-births at each hospital, excluding delivery after maternal transfer. The incidence was calculated for inborn cases only.

2.5. Impact of national guidelines

To determine the effect of the Japanese national guidelines issued in June 2008, we divided the study period into two periods, before (2004–2008, first period) and after (2009–2010, second period) the guidelines.

2.6. Statistics

Differences between categorical variables were assessed using the Chi-square test, with Yates' correlation when appropriate. For the assessment of differences between nominal variables, the Student's *t*-test or the Mann–Whitney *U*-test was used. *p*-Values of <0.05 were considered significant. SSPS for Windows (version 19.0, SPSS Inc., Chicago, IL) was used to perform the statistical analysis.

3. Results

One hundred fifty-two hospitals participated in this study (see Appendix). Of these, 14 hospitals managed only outborn infants because of the absence of an obstetric department. Of the remaining 138 hospitals, 62 had neonatal intensive care units and 76 were regional centers.

3.1. Study populations and demographic features

During the 7-year study period, 88 EOD and 162 LOD cases were reported. Baseline data are shown in Table 1. Maternal age of EOD infants (31.0 ± 5.0 years) was significantly older than that of LOD infants (29.4 ± 4.5 years) ($p < 0.001$). All values other than maternal age in Table 1 did not differ significantly between EOD and LOD infants. The age distribution at diagnosis and gestational age at birth are shown in Figure 1. The median age of LOD infants was 28.5 days (range 7–88 days), and 80 of 88 EOD cases were diagnosed at 0–2 days. Preterm births included 25.0% EOD and 28.4% LOD infants.

3.2. Serotype distribution

Among 64 isolates serotyped, the distribution was Ia ($n = 7$), Ib ($n = 1$), III ($n = 8$), V ($n = 1$), VI ($n = 1$), and VIII ($n = 1$) in EOD, and Ia ($n = 13$), Ib ($n = 6$), III ($n = 24$), IV ($n = 1$), and V ($n = 1$) in LOD.

3.3. Characteristics of infants with group B streptococcal disease

The initial symptoms, diagnosis, GBS isolation site, and outcome are shown in Table 2. The presentation of shock was highly associated with a fatal outcome (5/9 in EOD and 2/4 in LOD). The most common diagnosis in EOD was sepsis, followed by meningitis and pneumonia. Among LOD cases, meningitis and sepsis were common, followed by arthritis (three cases involved hip joints and one case involved the knee joint) and cellulitis (three involved inguinal regions, one the buttock region, and one involved the cervical region).

The case fatality of EOD was 13.6%, which was much higher than that of LOD (8.0%), however the difference did not reach significance (Table 2). When the study period was divided into the two periods mentioned above, mortality declined from 14.8% (8/54) in the first period to 11.8% (4/34) in the second period among EOD, and from 9.8% (11/112) to 2.5% (2/50) among LOD. Case fatality in total was significantly higher in infants born prematurely: 21.3% (10/47) at ≤33 weeks of gestation, 15.0% (3/20) at 34–36 weeks of gestation, and 4.9% (9/183) at ≥37 weeks of gestation (Chi-square for trend $p < 0.001$). This significance was observed in EOD cases (40.9% (9/22) in preterm vs. 4.5% (3/66) in term babies; $p < 0.001$; odds ratio 14.3, 95% confidence interval (CI) 3.5–61.2), while not in LOD cases (8.7% (4/46) in preterm vs. 7.8% (9/116) in term babies). Similarly, case fatality was significantly associated with birth weight in infants with EOD (37.5% (9/24) <2500 g vs. 4.7% (3/64) ≥2500 g, $p < 0.001$; odds

Table 1
Baseline characteristics of infants with early-onset and late-onset group B streptococcal disease

	Early-onset disease (EOD), $n = 88$	Late-onset disease (LOD), $n = 162$
Male:female	50:38	89:73
Birth weight (g), for 88 EOD, 160 LOD		
Median/range	3020/556–4340	2849/435–3804
Low birth weight (<2500 g)	21 (23.9%)	50 (30.9%)
Very low birth weight (1000–1499 g)	5	12
Extremely low birth weight (<1000 g)	8	11
Gestational age (weeks)		
Median/range	39/22–42	38/22–42
Preterm births (<37 weeks)	22 (25.0%)	46 (28.4%)
Early preterm births (22–33 weeks)	18	29
Late preterm births (34–36 weeks)	4	17
Twins	3	9
Maternal age[a] (years), for 82 EOD, 115 LOD		
Mean ± SD	31.1 ± 5.0	29.4 ± 4.5
Median/range	32/22–42	30/19–39
<20 years	0	1
Cesarean sections, for 88 EOD, 151 LOD	18 (20.5%)	51 (33.8%)
Mothers with ≥1 risk factors	30 (34.1%)	48 (29.6%)
Prematurity	21	48
Intrapartum fever	10	1
Premature rupture of membranes	5	1
Previous sibling with GBS disease	0	0
Birth place		
Hospital without maternal transfer (inborn cases)	36	42
Hospital within 2 weeks after maternal transfer (maternal transfer cases)	7	15
Hospital or clinic other than managed center (outborn cases)	44	105
Home	1	0

SD, standard deviation.
[a] $p < 0.001$ (EOD vs. LOD).

ratio 12.2, 95% CI 2.9–50.7), but not in those with LOD (12.2% (6/49) <2500 g vs. 6.2% (7/113) ≥2500 g). Mortality in EOD did not differ among birth places: 13.9% (5/36) in inborn cases, 28.6% (2/7) in maternal transfer cases, and 11.1% (5/45) in outborn cases.

As for morbidity, EOD and LOD cases had sequelae in 13.6% and 21.0%, respectively (Table 2). The morbidity rate was not different between preterm and term neonates. A high rate of neurological sequelae was noted in meningitis in EOD (33.3%, 8/24) and LOD (34.1%, 29/85; $p < 0.001$ vs. non-meningitis LOD (6.6%, 5/76)) cases. Speech or mental delay ($n = 23$), epilepsy ($n = 13$), cerebral palsy ($n = 9$), brain atrophy ($n = 7$), hydrocephalus ($n = 4$), visual impairment ($n = 3$), and deafness ($n = 2$) were documented. Cellulitis and arthritis had an excellent prognosis without any fatality or complications.

Of 88 EOD, 51 (58.0%) mothers underwent culture screening during pregnancy at any time, 20 did not, and for 17 this was unknown. Nine of 25 mothers whose culture time was known were screened before 33 weeks of gestation, i.e., in an inappropriate period according to the Japanese guidelines. The majority (28/51) of mothers were screened GBS-negative and 23 were positive; however, culture results did not affect the mortality or morbidity of the 51 EOD infants whose mothers underwent culture screening.

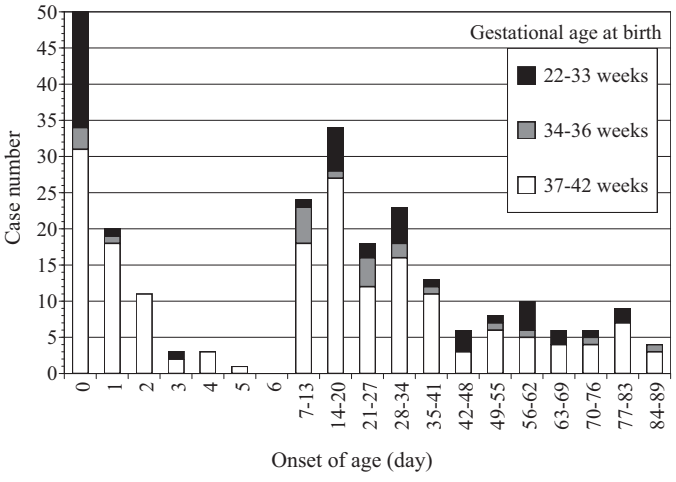

Figure 1. Age distribution at disease onset and gestational age at birth.

3.4. Implementation of prophylaxis guideline

The time when prophylaxis guidelines were introduced differed among the hospitals. Figure 2 shows the cumulative change in the introduction in 138 hospitals that had a department of obstetrics. The rate was 42.0% (58/138) at the start of the study in January 2004, and rapidly increased in 2008, when the national guidelines were issued. At the end of the study, more than 90% (125/138) of the hospitals had adopted the guidelines. Among 36 inborn EOD cases, 27 were born at institutions after guideline introduction, and nine were born before their introduction; however, the mortality of the 36 inborn cases did not differ between individuals born at hospitals before (11%, 1/9) or after (11%, 3/27) the adoption of a preventive strategy.

3.5. Incidence of EOD and LOD

Finally, we attempted to assess the incidence of EOD and LOD. The total number of live-births as defined above was 438 359 in the 138 hospitals between 2004 and 2010. The EOD and LOD inborn cases numbered 36 and 42, respectively. Thus, the estimated incidence of EOD and LOD were 0.08 (95% CI 0.06–0.11)/1000 live-births and 0.10 (95% CI 0.07–0.12)/1000 live-births, respectively. No significant differences were observed in the EOD and LOD incidence between the first period (0.08 (95% CI 0.05–0.10)/1000 live-births, 23/305 210, and 0.10 (95% CI 0.06–0.13)/1000 live-births, 29/305 210) and the second period (0.10 (95% CI 0.07–0.12)/1000 live-births, 13/133 329, and 0.10 (95% CI 0.07–0.12)/1000 live-births, 13/133 329), respectively.

Table 2
Characteristics of infants with group B streptococcal disease

	Early-onset disease (EOD), $n = 88$	Late-onset disease (LOD), $n = 162$
Initial symptoms[a]		
Fever	31 (35.2%)	106 (65.4%)
Respiratory (apnea, grunting, respiratory distress, and/or retraction)	57 (64.8%)	51 (31.5%)
Central nervous system (convulsions and/or altered consciousness)	18 (20.5%)	18 (11.1%)
Vomiting	3 (3.4%)	9 (5.6%)
Shock	9 (10.2%)	4 (2.5%)
Diagnosis		
Sepsis	55 (62.5%)	65 (40.1%)
Meningitis[b]	24 (27.3%)	85 (52.5%)
Pneumonia	9 (10.2%)	3 (1.9%)
Arthritis	0	4 (2.5%)
Cellulitis	0	5 (3.1%)
Bacterial isolation site		
Blood alone	64 (72.7%)	73 (45.1%)
CSF + blood	19 (21.6%)	73 (45.1%)
CSF alone	5 (5.7%)	12 (7.4%)
Joint + blood	0	2 (1.2%)
Joint alone	0	2 (1.2%)
Outcome		
Died	12 (13.6%)	13 (8.0%)
Survived with sequelae	12 (13.6%)	34 (21.0%)

CSF, cerebrospinal fluid.
[a] Each infant had one or more symptoms.
[b] Cases with group B Streptococcus isolation from both blood and CSF are classified as meningitis.

4. Discussion

In this study, we detail the epidemiology of infantile invasive GBS infections between 2004 and 2010 in Japan. This is of note because data from Asian countries are sparse. One of the important findings derived from this study are the remaining high mortality and morbidity rates. The case fatality rates of 13.6% in EOD and 8.0% in LOD are comparable with recent global data showing the mean rates in EOD and LOD to be 12.1% (95% CI 6.2–18.3) and 6.8% (95% CI 4.3–9.4), respectively.[4] However, our data are slightly higher than those in the USA and high-income European countries.[4,6,10–14] When our study period is limited to 2009–2010, fatality improved in EOD (11.8%) and LOD (2.5%).

We examined the association of several perinatal factors with mortality. As in previous papers,[10,14] prematurity and low birth weight were significantly linked to early-onset mortality. Furthermore, we hypothesized that transfer EOD cases would have a poor prognosis, since there is evidence of an association between the duration of transport and increased mortality. A cohort study of 4966 transferred neonates in Osaka, Japan, showed that those transported for >90 min had twice the rate of neonatal death compared with those transported for between 30 and 59 min.[17] However, our study did not show a significant effect of different birth place on the prognosis, suggesting that the perinatal transfer network in Japan is functional.

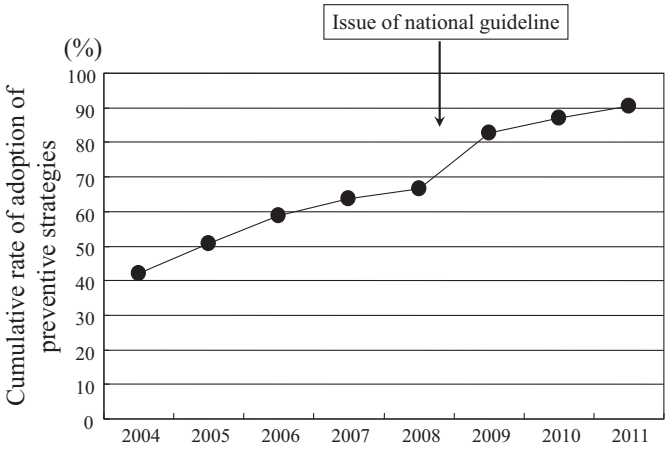

Figure 2. Cumulative rate of adoption of preventive strategies in January each year among 138 hospitals with a department of obstetrics.

Neurological sequelae were found in approximately a third of infants with meningitis. This proportion is also comparable to that of recently published studies, which have usually included moderate to severe sequelae;[18] however, the morbidity rate may increase after long-term follow-up because cognitive impairment and subtle neurodevelopmental and behavioral delay may be identified later. In fact, neurological sequelae have been shown to increase to as high as 44–50% of GBS meningitis at the age of 5–6 years when mild disability is included in the analysis.[19,20]

Another important finding is an apparent low incidence of EOD and LOD, which were stable from the first to second study periods. It is possible that GBS disease is underestimated since systematic cultures are not performed, and there can be false-negative cultures related to the very small volume of blood inoculated. Alternatively, the low rates could be due to high levels of transplacentally acquired protective antibodies in cord serum.[21,22] In addition, the low rates may reflect the prevalence of less virulent strains. This and previous studies[15,23,24] indicate that serotypes VI and VIII predominate among pregnant women carriers in Japan, while these strains are rarely isolated from EOD neonates. Ethnic factors may also have a role in susceptibility to GBS disease.

We should acknowledge the limitations in these estimates since they were not population-based but institution-based in a retrospective study. Neonatal GBS incidence based on capture–recapture analysis has been reported in a nationwide fashion from European countries.[10–12] However, the function and location of the hospitals participating in this study varied widely, and one or more institutions were enrolled from 44 of 47 prefectures in Japan. We therefore believe that there is minimal bias in enrollment. Moreover, national statistics have indicated that the early neonatal mortality rate due to perinatal infections was 2.3–2.7/100 000 live-births in 2004–2010.[16] Assuming that 40% of the fatal etiology is attributable to GBS,[25] 0.9–1.1/100 000 live-births die as a result of this pathogen. This figure is concordant with the EOD death rate of 1.1/100 000 live-births in our analysis. Thus, national statistics[16] support the validity of our estimates.

In summary, this is the first study to show the nationwide epidemiology of infantile GBS disease in Japan. Our results reveal a very low incidence of EOD and LOD, but mortality and morbidity rates remain substantial. There are significant associations between EOD case fatality and prematurity as well as low birth weight, and between sequelae and the diagnosis of meningitis. National guidelines have had no effect on the incidence of EOD but have improved the prognosis. This study may serve as a baseline for the development and implementation of further evidence-based guidelines. We have planned a prospective, population-based GBS case enrollment in Japan to more precisely determine the epidemiology of GBS diseases.

Acknowledgements

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Conflict of interest: The authors have no conflicts of interest to declare.

Appendix A

A.1. Participating hospitals, n = 152

Hokkaido Medical Center for Child Health and Rehabilitation, Sapporo, Hokkaido; Sapporo Social Insurance General Hospital, Sapporo, Hokkaido; Sapporo Tokushukai Hospital, Sapporo, Hokkaido; Sapporo Hokuyu Hospital, Sapporo, Hokkaido; Nikko Memorial Hospital, Muroran, Hokkaido; Hakodate Municipal Hospital, Hakodate, Hokkaido; Asahikawa Medical University, Asahikawa, Hokkaido; Kushiro Red Cross Hospital, Kushiro, Hokkaido; Tomakomai City Hospital, Tomakomai, Hokkaido; Engaru-Kosei General Hospital, Monbetsu, Hokkaido; Kuroishi General Hospital, Kuroishi, Aomori; National Hirosaki Hospital, Hirosaki, Aomori; Sendai City Hospital, Sendai, Miyagi; Saka General Hospital, Shiogama, Miyagi; Yamagata City Hospital Saiseikan, Yamagata; Iwate Medical University, Morioka, Iwate; Odate Municipal General Hospital, Odate, Akita; Fukushima Medical University, Fukushima; Gunma University Hospital, Maebashi, Gunma; Gunma Children's Medical Center, Shibukawa, Gunma; Jichi Medical University, Shimono, Tochigi; Ibaraki Seinan Medical Center Hospital, Sashima-gun, Ibaraki; Hitachi General Hospital, Hitachi, Ibaraki; Saitama City Hospital, Saitama; Saitama Medical Center, Kawagoe, Saitama; Koshigaya Municipal Hospital, Koshigaya, Saitama; Kameda Medical Center, Kamogawa, Chiba; Chiba Aoba Municipal Hospital, Chiba; Chiba Kaihin Municipal Hospital, Chiba; Nippon Medical School, Chiba Hokusoh Hospital, Inzai, Chiba; Sakura Hospital, Toho University Medical Center, Sakura, Chiba; Teikyo University Chiba Medical Center, Ichihara, Chiba; Matsudo City Hospital, Matsudo, Chiba; Tokyo Women's Medical Center, Yachiyo Medical Center, Yachiyo, Chiba; Asahi General Hospital, Asahi, Chiba; Toranomon Hospital, Minato-ku, Tokyo; Teikyo University School of Medicine, Itabashi-ku, Tokyo; Showa University School of Medicine, Shinagawa-ku, Tokyo; Tokyo Metropolitan Bokutoh Hospital, Sumida-ku, Tokyo; Tokyo Women's Medical University Medical Center East, Arakawa-ku, Tokyo; Tokyo Teishin Hospital, Chiyoda-ku, Tokyo; Toho University Medical Center Omori Hospital, Ohta-ku, Tokyo; Juntendo University School of Medicine, Bunkyo-ku, Tokyo; Tokyo Metropolitan Children's Medical Center, Fuchuu, Tokyo; Tokyo Nishi Tokushukai Hospital, Showa, Tokyo; Nippon Medical School, Taga Nagayama Hospital, Tama, Tokyo; Tama-Hokubu Medical Center, Higashimurayama, Tokyo; Saiseikai Yokohamashi Nanbu Hospital, Yokohama, Kanagawa; Yokohama City University Medical Center, Yokohama, Kanagawa; St. Marianna University, School of Medicine, Yokohama-City Seibu Hospital, Yokohama, Kanagawa; Showa University Fujigaoka Hospital, Yokohama, Kanagawa; Odawara Municipal Hospital, Odawara, Kanagawa; National Hospital Organization Kanagawa Hospital, Hadano, Kanagawa; Nippon Medical School Musashi Kosugi Hospital, Kawasaki, Kanagawa; Teikyo University School of Medicine, Mizonokuchi Hospital, Kawasaki, Kanagawa; Yokosuka City Hospital, Yokosuka, Kanagawa; National Hospital Organization Sagamihara National Hospital, Sagamihara, Kanagawa; Kofu Kyoritsu Hospital, Kofu, Yamanashi; Kashiwazaki General Hospital and Medical Center, Kashiwazaki, Niigata; Nagano Red Cross Hospital, Nagano; Shinshu University, School of Medicine, Matsumoto, Nagano; Nagano Children's Hospital, Azumino, Nagano; Saku Central Hospital, Saku, Nagano; Iida Municipal Hospital, Iida, Nagano; Shizuoka Red Cross Hospital, Shizuoka; Juntendo University Shizuoka Hospital, Izunokuni, Shizuoka; Iwata City Hospital, Iwata, Shizuoka; Shimada Municipal Hospital, Shimada, Shizuoka; Chuubu Rosai Hospital, Nagoya, Aichi; Nagoya University Hospital, Nagoya, Aichi; Meitetsu Hospital, Nagoya, Aichi; Nagoya City University Hospital, Nagoya, Aichi; Nagoya Ekisaikai Hospital, Nagoya, Aichi; Nagoya Daini Red Cross Hospital, Nagoya, Aichi; Aichi Prefectural Colony Central Hospital, Kasugai, Aichi; Hekinan Municipal Hospital, Hekinan, Aichi; Komaki City Hospital, Komaki, Aichi; Aichi Children's Health and Medical Center, Obu, Aichi; Toyota Kosei Hospital, Toyota, Aichi; Toyota Memorial Hospital, Toyota, Aichi; Okazaki City Hospital, Okazaki, Aichi; Gifu Prefectural General Medical Center, Gifu; Tajimi Hospital, Tajimi, Gifu; Takayama Red Cross Hospital, Takayama, Gifu; National Mie Hospital, Tsu, Mie; Ishikawa Prefectural Central Hospital, Kanazawa, Ishikawa; National Hospital Organization Iou National Hospital, Kanazawa, Ishikawa; Toyama Prefectural Central Hospital, Toyama; Faculty of Medical Science, University of Fukui, Yoshida-gun, Fukui; Fukui Prefectural Hospital, Fukui; Fukui Red Cross Hospital, Fukui; Saiseikai Shigaken Hospital, Ritto, Shiga; Ohtsu Red Cross Hospital, Ohtsu, Shiga; Takashima Municipal Hospital, Takashima, Shiga; Kyoto City Hospital, Kyoto; Kyoto Katsura Hospital, Kyoto; Japan Baptist Hospital, Kyoto; Social Insurance Kyoto Hospital, Kyoto; Kyoto University Hospital, Kyoto; Japanese Red Cross Kyoto Daiichi Hospital, Kyoto; National Hospital Organization Kyoto Medical Center, Kyoto; Osaka City University Hospital, Osaka; Nakano Children's Hospital, Osaka; Nissei Hospital, Osaka; Chibune Hospital, Osaka; Osaka Red Cross Hospital, Osaka; Yodogawa Christian Hospital, Osaka; Kitano Hospital, Osaka; Matsushita Memorial Hospital, Moriguchi, Osaka; Toyonaka Municipal Hospital, Toyonaka, Osaka; Hoshigaoka Koseinenkin Hospital, Hirakata, Osaka; Minoh City Hospital, Minoh, Osaka; Komatsu Hospital, Neyagawa, Osaka; Itami City Hospital, Itami, Osaka; Japanese Red Cross Wakayama Medical Center, Wakayama; Naga Hospital, Kinokawa, Wakayama; Yamato Takada Municipal Hospital, Yamatotakada, Nara; Tenri Yorozu Hospital, Tenri, Nara; Nishi-Kobe Medical Center, Kobe, Hyogo; Kobe City Medical Center General Hospital, Kobe, Hyogo; Hyogo Prefectural Tsukaguchi Hospital, Amagasaki, Hyogo; Himeji Red Cross Hospital, Himeji, Hyogo; Ono Municipal Hospital, Ono, Hyogo; Hyogo Prefectural Nishinomiya Hospital, Nishinomiya, Hyogo; Kawasaki Medical School, Kurashiki, Okayama; Kurashiki Medical Center, Kurashiki, Okayama; Kurashiki Central Hospital, Kurashiki, Okayama; Tsuchiya General Hospital, Hiroshima; Hiroshima City Funairi Hospital, Hiroshima; Onomichi General Hospital, Onomichi, Hiroshima; Tottori Prefectural Central Hospital, Tottori; Shimane Prefectural Central Hospital, Izumo, Shimane; Takamatsu Red Cross Hospital, Takamatsu, Kagawa; Kagawa Prefectural Central Hospital, Takamatsu, Kagawa; Tokushima Red Cross Hospital, Komatsujima, Tokushima; Kochi Health Sciences Center, Kochi; Kyushu University Hospital, Fukuoka;

National Hospital Organization, Kyushu Medical Center, Fukuoka; National Hospital Organization, Fukuoka Hospital, Fukuoka; National Hospital Organization, Kokura Medical Center, Kitakyushu, Fukuoka; Kyushu Kosei Nenkin Hospital, Kitakyushu, Fukuoka; Fukuoka University Chikushi Hospital, Chikushi, Fukuoka; Iizuka Hospital, Iizuka, Fukuoka; National Hospital Organization Fukuoka Higashi Medical Center, Koga, Fukuoka; Takagi Hospital, Okawa, Fukuoka; National Hospital Organization, Saga Hospital, Saga; Nagasaki Municipal Hospital, Nagasaki; Oita University, Faculty of Medicine, Oita; Kumamoto Central Hospital, Kumamoto; Kagoshima Municipal Hospital, Kagoshima; Kagoshima Seikyo Hospital, Kagoshima; Okinawa Red Cross Hospital, Naha, Okinawa.

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