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by Yusuke Tsumura, Hideki Muramatsu, Nobuyuki Tetsuka, Takahiro Imaizumi, Kikue Sato, Kento Inoue, Yoshitomo Motomura, Yuko Cho, Daiki Yamashita, Daichi Sajiki, Ryo Maemura, Ayako Yamamori, Masayuki Imaya, Manabu Wakamatsu, Kotaro Narita, Shinsuke Kataoka, Motoharu Hamada, Rieko Taniguchi, Eri Nishikawa, Atsushi Narita, Nobuhiro Nishio, Seiji Kojima, Yoshihiko Hoshino, and Yoshiyuki Takahashi

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A Japanese retrospective study of non-tuberculous mycobacterial infection in children, adolescents, and young adult patients with hematologic-oncologic diseases

Yusuke Tsumura,[1] Hideki Muramatsu,[†1] Nobuyuki Tetsuka,[2] Takahiro Imaizumi,[3] Kikue Sato,[4] Kento Inoue,[5] Yoshitomo Motomura,[6] Yuko Cho,[7] Daiki Yamashita,[1] Daichi Sajiki,[1] Ryo Maemura,[1] Ayako Yamamori,[1] Masayuki Imaya,[1] Manabu Wakamatsu,[1] Kotaro Narita,[1] Shinsuke Kataoka,[1] Motoharu Hamada,[1] Rieko Taniguchi,[1] Eri Nishikawa,[1] Atsushi Narita,[1] Nobuhiro Nishio,[1] Seiji Kojima,[1] Yoshihiko Hoshino,[8] and Yoshiyuki Takahashi[†1]

[1]Department of Pediatrics, Nagoya University Graduate School of Medicine, Nagoya, Japan

[2]Department of Infection Control, Gifu University Graduate School of Medicine, Gifu, Japan

[3]Department of Advanced Medicine, Nagoya University Hospital, Nagoya, Japan

[4]Medical IT Center, Nagoya University Hospital, Nagoya, Japan

[5]Department of Pediatrics and Developmental Biology, Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental University, Tokyo, Japan

[6]Department of Pediatrics, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan

[7]Department of Pediatrics, Hokkaido University Hospital, Sapporo, Japan

[8]Department of Mycobacteriology, Leprosy Research Center, National Institute of Infectious Diseases, Tokyo, Japan

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Corresponding authors:

Hideki Muramatsu, M.D., Ph.D.

Department of Pediatrics, Nagoya University Graduate School of Medicine, 65 Tsurumai-cho, Showa-ku, Nagoya, Aichi 466-8560, Japan

Email: hideki-muramatsu@med.nagoya-u.ac.jp

Tel: +81-52-741-2111; Fax: +81-52-744-2974

Yoshiyuki Takahashi, M.D., Ph.D.

Department of Pediatrics, Nagoya University Graduate School of Medicine, 65 Tsurumai-cho, Showa-ku, Nagoya, Aichi 466-8560, Japan

E-mail: ytakaha@med.nagoya-u.ac.jp

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Data sharing statement: The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Abstract

Non-tuberculous mycobacterial infection (NTM) is rare in healthy children, with lymphadenitis being the most common presentation. Immunocompromised populations are known to be at high risk, but the clinical picture of NTM infection in pediatric hematology/oncology patients is unclear. In this nationwide retrospective analysis of patients under the age of 40 treated in Japanese pediatric hematology/oncology departments who developed NTM infection between January 2010 and December 2020, 36 patients (21 patients with hematopoietic stem cell transplantation (HSCT) and 15 nontransplant patients) were identified. Post-transplant patients were infected with NTM at 24 sites, including the lungs (n = 12), skin and soft tissues (n = 6), bloodstream (n = 4), and others (n = 2). Nine of twelve patients with pulmonary NTM infection had a history of pulmonary graft-versus-host disease (GVHD), and rapid-growing mycobacteria (RGM) were isolated from five of them. In nontransplant patients, the primary diseases were acute lymphoblastic leukemia (ALL; n = 5), inborn errors of immunity (IEI; n = 6), and others (n = 4). All cases of ALL had bloodstream infections with RGM, whereas all cases of IEI were infected with slow-growing mycobacteria (SGM). In summary, three typical clinical scenarios for pediatric hematology/oncology patients have been established: RGM-induced pulmonary disease in patients with pulmonary GVHD, RGM bloodstream infection in patients with ALL, and SGM infection in patients with IEI. Our findings suggest that NTM must be regarded as a pathogen for infections in these high-risk patients, especially those with pulmonary GVHD, who may require active screening for NTM.

Introduction

Non-tuberculous mycobacteria (NTM) were first identified in the 1950s as human pathogenic acid-fast bacilli (1) and now involve up to 200 species, excluding *M. tuberculosis* complex and *M. leprae*. They are classified based on their growth rate in solid agar into two major groups: rapid-growing mycobacteria (RGM) and slow-growing mycobacteria (SGM).(1, 2)

According to recent studies from various regions, the incidence and prevalence of NTM pulmonary infection—the most common form of NTM infection—in the general population are estimated to be 18–45 per 100,000 person-years and 15–57 per 100,000 people, respectively.(3-6) Epidemiological data show that NTM infection has been increasing worldwide in recent years,(7, 8) and in some countries, including Japan, the infection rate of NTM has surpassed that of tuberculosis.(4, 9) The high-risk groups for NTM infection include the elderly, patients with cystic fibrosis (CF), and immunocompromised individuals due to various factors such as human immunodeficiency virus infection, inborn errors of immunity (IEI), chemotherapy, and post organ transplantation.(7)

NTM infections are extremely rare in children, with an incidence of 0.6–2.2 per 100,000 person-years in the general pediatric population, with the majority occurring under the age of 5 and involving lymph nodes.(10, 11) However, even among children, patients with IEI can develop disseminated NTM infections involving multiple sites such as the lung, bloodstream, and skin/soft tissue, and patients with CF are at high risk for pulmonary NTM infection.(12-14) In addition, a variety of NTM infections in pediatric hematology/oncology patients with theoretical defects in immunity have been reported.(15-19) However, previous reports have only focused on specific NTM infection sites or species, and there have been no nationwide single-cohort studies

that provide a comprehensive view of NTM infection in pediatric hematology/oncology patients.(17, 20-22) Thus, there is little evidence that differences in underlying diseases, treatments, and complications could influence the nature of NTM infections in this entity.

To assess the overall clinical features of NTM infection in pediatric hematology/oncology patients, this retrospective multicenter study was conducted involving 121 pediatric hematology/oncology institutions in Japan, and the NTM incidence in pediatric hematology/oncology patients was estimated using data from the Japanese public registries.

Methods

Patients

In this study, patients under the age of 40 years with hematologic diseases, malignancies, and IEI who developed NTM infection between January 2010 and December 2020 were studied retrospectively. Patients already diagnosed with NTM infection at the start of the study or those with relapse or reinfection were excluded. A questionnaire was sent to 121 pediatric hematology/oncology institutions throughout Japan asking about their experience with NTM-infected patients (**Supplemental Figure 1**). Of these 121 institutions, 22 provided clinical data on 36 patients with NTM, while the remaining 99 institutions had no patients diagnosed with NTM during the study period. Details of questionnaire are provided in the **Supplemental Methods**. This study was approved by the Ethics Committee of the Nagoya University Graduate School of Medicine. An opt-out consent process was approved by disseminating the research information; thus, the requirement of informed consent was waived.

NTM diagnosis, classification, and treatment

Specimens for microbiological testing were collected at the discretion of each institution. In this study, pulmonary NTM infections were diagnosed using the latest American Thoracic Society/Infectious Diseases Society of America criteria and evaluated their certainty according to a previous study.(17, 23, 24) In addition, extrapulmonary NTM infections were defined as one or more positive culture or polymerase chain reaction results indicating active infection from normally sterile sites (muscle, joints, bone marrow, and blood, including the central venous line). Disseminated lesions were defined as evidence of NTM infection at two or more different sites. We defined the date of treatment completion as the date of the last dose of medication after 1 year had passed without NTM relapse.

NTM isolation and identification

Detailed information on NTM cultured, isolated, and identified from clinical specimens at each institution was collected using the aforementioned questionnaire (**Supplemental Methods**).

Statistical analysis

A two-sided Fisher's exact test was used to compare categorical variables. The probabilities of event-free survival and overall survival (OS) were calculated using the Kaplan–Meier method, and the log-rank test was used to compare the two groups. The probabilities of treatment completion for NTM were estimated using cumulative incidence methods, and the Gray test was used to compare the two groups. The treatment completion for NTM infection was defined as the event of interest with death from any cause as a competing event. A p-value of <0.05 was considered statistically significant. Details of other statistical methods and software libraries used for analysis and plotting are described in the **Supplemental Methods**.

Estimation of NTM infection incidence

The Japanese Society of Pediatric Hematology/Oncology (JSPHO) patient registry (https://www.jspho.org/disease_record_en.html) and the Japanese Data Center for Hematopoietic Cell Transplantation (JDCHCT) registry(25) are both Japanese nationwide registries of children with hematology/oncology disorders and HSCT recipients, respectively. Using the number of patients enrolled in these registries from 2015–2019 as the denominator, the incidence of NTM infections was estimated in children and adolescents (0–19 years) with malignancies (n = 16) or those receiving allogeneic HSCT (n = 17) during the same period (2015–2019) in the current study.

Results

Patient characteristics

From January 2010 to December 2020, 36 child, adolescent, and young adult patients (18 males and 18 females) with hematologic malignancies, extracranial solid tumors, benign hematological disorders, or IEI, and developing NTM infection were identified from 22 institutes throughout Japan (**Figures 1 and 2A and Supplemental Figures 2A and 2B**). The patient characteristics are summarized in **Table 1**. The underlying diseases were hematologic malignancies (n = 19), benign hematological disorders (n = 4), solid tumors (n = 2), and IEI (n = 11), with 21 patients (58%) receiving HSCT. The median age of the entire cohort at the time of NTM infection diagnosis was 13 years (range, 3–24 years).

NTM infections in pediatric hematology/oncology patients

The NTM species were identified in 34 of 36 pediatric hematology/oncology patients with NTM infections. At the time of diagnosis, one patient had multiple NTM species, and three others had other infections of different NTM species during the initial NTM infection treatment course. In total, 39 NTM strains isolated from 34 patients were

species-identified, with 18 SGM and 21 RGM (**Figure 1 and Supplemental Figure 3**). Notably, *M. avium* complex (MAC) was the most frequently isolated species from the SGM-infected cases (11 strains; five strains of *M. avium,* five strains of *M. intracellulare,* and one strain that could not be identified further than MAC), followed by *M. kansasii* (four strains), and *M. gordonae*, *M. parascrofulaceum*, and *M. marseillense* (one strain each). On the contrary, *M. abscessus* complex was the most frequently isolated species from the RGM-infected cases (10 strains), followed by *M. chelonae* (five strains), *M. fortuitum* (four strains), and *M. mucogenicum* (two strains). In terms of infection sites, 28 patients had single-site infections (definite pulmonary [n = 12], probable pulmonary [n = 3], skin and soft tissue [n = 4], catheter-related bloodstream infection [CRBSI; n = 4], and other bloodstream infections [n = 5]), and eight had disseminated infections (**Figure 1**).

Characteristics of NTM infections in patients receiving HSCT

In this cohort, there were 21 patients with NTM infection who underwent HSCT regardless of the underlying disease (**Figure 1 and Supplemental Table 1**). There were 24 infection sites, including the lungs (n = 12), skin and soft tissues (n = 6), bloodstream (n = 4), bone marrow (n = 1) and joint (n =1). The infection was localized in 17 cases and disseminated in four. Furthermore, 14 patients had Grade II–IV acute GVHD, 14 had chronic GVHD, and 11 had pulmonary GVHD. All patients received immunosuppressive agents, with 19 receiving steroids.

RGM strains (*M. abscessus* [n = 8], *M. chelonae* [n = 4], *M. mucogenicum* [n = 1], and *M. fortutium* [n = 1]) were isolated from 13 patients, SGM strains (MAC [n = 5], *M. kansasi* [n = 3], and *M. gordonae* [n = 1]) from nine patients, and both RGM (*M. abscessus*) and SGM (MAC) from one patient. Among 12 patients with pulmonary infection, *M. abscessus* was isolated from eight patients and MAC from four patients.

In contrast, among six patients with skin and soft tissue infections, *M. chelonae* was isolated from three patients and *M. kansasii* from three patients (**Figure 1**). Regarding the duration from transplantation to the onset of NTM infection, RGM infections occurred significantly earlier than SGM infections (10.1 months vs. 39.5 months, p = 0.0018; **Figure 2B**).

Characteristics of NTM infections in patients who had not received HSCT in the past

In the current cohort, 15 patients with no prior HSCT had an NTM infection. The underlying diseases were acute lymphoblastic leukemia (ALL; n = 5), IEI (n = 6), and others (Hodgkin's lymphoma, Castleman disease, Ewing sarcoma, and neuroblastoma in one case each) (**Figure 1**). All patients with ALL had bloodstream RGM infections (four of which were catheter-related), while all patients with IEI had SGM, with MAC being isolated from five of them. The diagnoses of the six patients with IEI were all classified into disease subtypes with known mycobacterial susceptibility (GATA2 deficiency [n = 2], NEMO deficiency [n = 2], hyper immunoglobulin E syndrome [n = 1], and STAT1 gain-of-function [n = 1]).(26, 27) RGM infections occurred significantly earlier than SGM infections (3.7 vs. 104 months, p = 0.0079; **Figure 2C**).

Treatment outcomes

In our pediatric hematology/oncology patient cohort, there were no instances in which NTM infection was the primary cause of death. The 5-year OS for the entire cohort was 75% (95% confidence interval [CI]: 56–87), with transplant-related complications (n = 7) and primary disease progression (n = 1) being the leading causes of death (**Figure 3A**). The 5-year OS for the 21 NTM-infected patients with prior HSCT was 59% (95%

CI: 34–77), whereas no deaths were observed in the 15 patients without prior HSCT during the observation period (**Figure 3B**).

The 3-year cumulative incidence of treatment completion was 81% (95% CI: 62–91), with a median duration of treatment completion of 1.5 years (95% CI: 0.9–2.4) (**Supplemental Figure 4A**). While the median duration of treatment completion was longer with SGM (1.9 years) than with RGM (0.9 years), the 3-year treatment completion rates did not differ significantly between SGM (74%, 95% CI: 44–89) and RGM (66%, 95% CI: 22–89) (**Supplemental Figure 4B**). Similarly, cumulative treatment completion rates did not differ significantly, regardless of HSCT history or infection sites (**Supplemental Figures 4C and 4D**).

Antibiotic combinations used to treat NTM infection

In the entire cohort, 32 of 36 patients (89%) with NTM infection were treated with three or more antibiotics (**Supplemental Figure 5A**). The drug combinations for the top six most frequently used antibiotics in SGM and RGM are presented in **Figures 3C and 3D**, respectively, for each NTM species. In addition, detailed combination patterns for all antibiotics are shown in **Supplemental Figures 5B and 5C**. In cases of SGM infection, 12 of 15 cases were treated with regimens that included rifampicin/rifabutin, ethambutol, and macrolides (**Figure 3C**). However, macrolide-based regimens of three or more antimycobacterial agents were administered in 16 of 19 RGM-infected patients and in all 10 cases of *M. abscessus* infection (**Figure 3D**).

Estimated incidence of NTM infection in children with hematologic malignancies and extracranial solid tumors

From 2015 to 2019, the JSPHO registry enrolled 5,101 children and adolescents (aged 0–19 years) with hematologic malignancies (ALL [n = 2,333], acute myeloid leukemia [n = 770], and other hematologic malignancies [n = 1,998]) and extracranial

solid tumors (n = 3,484). At the same time, our nationwide retrospective cohort included 14 pediatric patients with hematologic malignancies and two with extracranial solid tumors (**Table 2)**. Based on these data, the incidences of NTM infection in children with hematologic malignancies and extracranial solid tumors were calculated to be 0.27% and 0.06%, respectively.

Estimated incidence of post-HSCT NTM infection in children

From 2015 to 2019, the JDCHCT registry enrolled 2,038 children (aged 0–19 years). At the same time, our nationwide retrospective cohort included 17 children with post-HSCT NTM infection (**Table 2)**. Based on these data, the incidence of NTM infection in pediatric recipients of HSCT was calculated to be 0.83% (**Table 2**).

Discussion

In this current nationwide retrospective study, NTM infection was identified in 36 child, adolescent, and young adult patients with hematologic malignancies, extracranial solid tumors, benign hematological disorders, or IEI. To the best of our knowledge, previous reports of NTM infections in pediatric hematology/oncology patients have been limited to literature reviews of small case series or single-center reports, with no cross-sectional analyses of a single cohort.(17, 20-22) While lymphadenitis with MAC is the canonical form of NTM infection in immunocompetent children, the current pediatric hematology/oncology cohort demonstrated a characteristic clinical picture, with a variety of SGM and RGM species infecting various sites.(10, 11) This cohort has revealed several clinical scenarios of NTM infections in this particular group of patients.

Our NTM cohort of 21 post-HSCT patients, which included 13 RGM and 8 SGM infections, revealed a skewed incidence in the early post-HSCT phase for RGM

and late for SGM (**Figure 2B**). Previous studies on HSCT adult recipients demonstrated that the incidence of NTM infection after transplantation ranged from 0.4% to 4.9%, with a median onset time ranging from 251 to 343 days.(28) This is roughly consistent with the incidence and median onset time of NTM infection in our pediatric cohort of 0.83% and 390 days, respectively, indicating that NTM infection should be noted even in children after transplantation. Furthermore, we have demonstrated for the first time, to the best of our knowledge, that the susceptible timing of infection differs between RGM and SGM, providing new insight into the infectious timeline after HSCT.(29)

Although pulmonary NTM was uncommon in healthy children, it was the most common form in our post-HSCT cohort. In this cohort, *M. abscessus* was the predominant pathogen, followed by MAC, accounting for 86% of all isolated species. These two species are also predominant in NTM infections of patients with CF (30), suggesting the presence of a common mechanism of NTM susceptibility in post-HSCT and CF cohorts. In fact, 9 of 12 post-HSCT patients (75%) with pulmonary NTM infection developed pulmonary GVHD. Because of the allogeneic immune response in pulmonary GVHD and recurrent infections in CF, the airways are exposed to persistent inflammation, resulting in pulmonary organization and bronchiectasis. To evaluate the incidence of NTM infection in patients with pulmonary GVHD, we estimated the number of patients with pulmonary GVHD based on the number of transplants obtained from the TRUMP registry and previous epidemiological data.(31-33) Using this as the denominator, the incidence of pulmonary NTM infection was calculated to be at least 5% in patients with pulmonary GVHD, comparable to the incidence in patients with CF, suggesting the need for aggressive NTM screening in patients with pulmonary GVHD.(13, 34)

In the non–HSCT group, our findings in patients with ALL and IEI were consistent with patterns reported in previous literature. Catheter- or non-catheter-related bloodstream infections associated with RGM have been reported sporadically in patients with ALL, while other forms of infection have been reported anecdotally.(20, 22) RGM is known for its ability to form biofilms and its high compatibility with artificial materials, both of which predispose to catheter infection.(35) In our cohort of five NTM-infected patients with ALL, all four patients with an identified species also had CRBSI due to RGM. In contrast, NTM infection in immunocompromised individuals has been previously studied in human immunodeficiency virus-infected adults and children with Mendelian susceptibility to mycobacterial disease, where MAC is predominantly isolated and infection patterns vary, including disseminated and pulmonary infections.(12, 36, 37) Although our cohort of IEI with NTM infection did not include classical Mendelian susceptibility to mycobacterial disease, disease subtypes in all six patients with IEI were reported to be susceptible to NTM.(26, 27, 38, 39) SGM was isolated from all six cases of IEI, five of which were MAC. Dissemination was observed in three cases and pulmonary disease in two. Thus, we established that CRBSI caused by RGM is a representative form of patients with ALL and that MAC-induced pulmonary disease and dissemination are the most common in IEI.

This study has some limitations due to the scarcity of prior research and its retrospective nature. First, there were no epidemiological data in the Japanese general pediatric population to serve as a reference point for specifying high-risk groups for NTM infections. Therefore, the estimated prevalence of NTM infection in Japanese children was calculated using a regional claim database and found to be equal to or lower than that of other countries (**Supplemental Table 2**).(10, 40) Second,

the incidence of NTM infection might be underestimated due to potential incomplete enrollment and undiagnosed cases at the institutions. Third, diagnostic methods and identification of NTM subspecies were based on institutional diagnosis and were not standardized. Finally, detailed subspecies-specific statistical analysis was insufficient because of the small number of cases due to rare infections in a rare population. However, single-cohort studies in the pediatric hematology/oncology field that provide an overview of NTM infection are scarce, and our study is one of the largest ever. In addition, even if potential underestimation is considered, our estimated high NTM incidence is still remarkable.

In conclusion, the current study identified high-risk groups of NTM infections in patients with pediatric hematology/oncology diseases and provided representative clinical pictures in each group. These findings may justify aggressive NTM screening in high-risk groups, which may improve diagnostic rates and reveal a more accurate clinical picture of NTM infections in pediatric hematology/oncology patients in the future.

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Tables

Table 1. Patient characteristics.

	Total cohort (N = 36)	With HSCT (n = 21)	Without HSCT (n = 15)
Sex (male/female)	18/18	10/11	8/7
Median age at NTM diagnosis, years (range)	13.6 (3–24.3)	14.5 (3–24.3)	9.0 (3.4–23.3)
Median duration from HSCT to onset of NTM infection, months (range)	-	13 (0.6–244.0)	-
Primary diagnosis			
Hematologic malignancies, n (%)	19 (51)	13 (62)	6 (40)
ALL	14	9	5
AML	3	3	0
JMML	1	1	0
HL	1	0	1
Solid tumors, n (%)	2 (5)	0 (0)	2 (13)
NBL	1	0	1
EWS	1	0	1
Non-malignant hematological diseases, n (%)	4 (11)	3 (14)	1 (7)
AA	2	2	0
DBA	1	1	0
Castleman syndrome	1	0	1
IEIs, n (%)	11 (32)	5 (24)	6 (40)
GATA2 deficiency	3	1	2
NEMO deficiency	2	0	2
IPEX syndrome	1	1	0
HIES	1	0	1
STAT1 GoF (T385M)	1	1	0
STAT2 GoF	1	0	1
XLP2	1	1	0
CGD	1	1	0

Abbreviations: AA, aplastic anemia; ALL, acute lymphoblastic leukemia; AML, acute myelogenous leukemia; CGD, chronic granulomatous disease; DBA, Diamond–Blackfan anemia; EWS, Ewing sarcoma; HIES, hyper–IgE syndrome; HL, Hodgkin lymphoma; HSCT, hematopoietic stem cell transplantation; IEI, inborn errors

of immunity; IPEX syndrome, immunodysregulation polyendocrinopathy enteropathy X-linked syndrome; JMML, juvenile myelomonocytic leukemia; NBL, neuroblastoma; NTM, non-tuberculous mycobacterium; STAT1 GoF, *STAT1* gain-of-function mutation; STAT2 GoF, *STAT2* gain-of-function mutation; XLP2, X-linked lymphoproliferative disease 2**.**

Table 2. Estimated incidence of NTM infection.

	Age group (year)	Study period (year)	Number of NTM cases	Denominator	Incidence (/100,000)
Hematologic malignancy	<20	2015−2019	14	JSPHO registry (n = 5,101)	275
Extracranial solid tumor	<20	2015−2019	2	JSPHO registry (n = 3,484)	57
Post-HSCT patient	<20	2015−2019	17	JDCHCT registry (n = 2,038)	834

Abbreviations: HSCT, hematopoietic stem cell transplantation; JDCHCT, Japanese Data Center for Hematopoietic Cell Transplantation; JSPHO, Japanese Society of Pediatric Hematology/Oncology; NTM, non-tuberculous mycobacterium.

Figure Legends

Figure 1. Clinical characteristics of 36 patients diagnosed with non-tuberculous mycobacterial infection in Japanese pediatric hematology/oncology institutions.

Each column represents one patient.

Abbreviations: AA, aplastic anemia; aGVHD, acute graft-versus-host disease; ALL, acute lymphoblastic leukemia; AML, acute myelogenous leukemia; CGD, chronic granulomatous disease; cGVHD, chronic graft-versus-host disease; DBA, Diamond–Blackfan anemia; EWS, Ewing sarcoma; HIES, hyper–IgE syndrome; HL, Hodgkin lymphoma; HSCT, hematopoietic stem cell transplantation; IEI, inborn errors of immunity; IPEX syndrome, immunodysregulation polyendocrinopathy enteropathy X-linked syndrome; JMML, juvenile myelomonocytic leukemia; NBL, neuroblastoma; NTM, non-tuberculous mycobacterium; STAT1 GoF, *STAT1* gain-of-function mutation; STAT2 GoF, *STAT2* gain-of-function mutation; UPN, unique patient number; WGS, whole genome sequencing; XLP2, X-linked lymphoproliferative disease 2.

Figure 2. Geographic distribution and duration from primary disease diagnosis to non-tuberculous mycobacterial infection (NTM) in Japanese pediatric hematology/oncology patients.

(A) The blue dots represent the locations of the 22 facilities where patients with NTM infections were identified. Black circles indicate the three Japanese megalopolis areas (Tokyo, Nagoya, and Osaka/Kyoto). (B) Box plots depict the time from hematopoietic stem cell transplantation to the onset of NTM infection in transplant cases. (C) Box

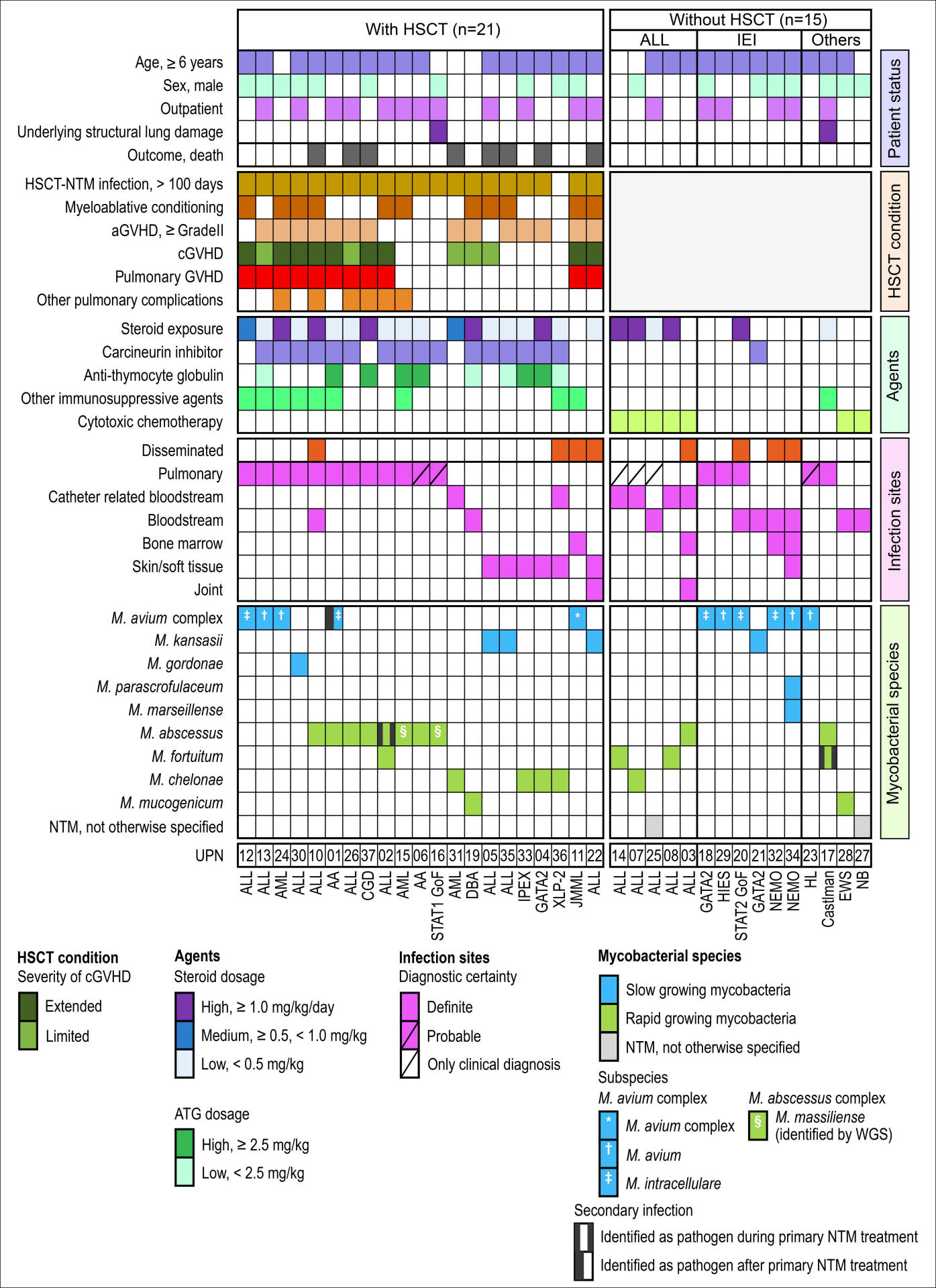
plots depict the time from primary disease diagnosis to NTM onset in nontransplant cases.

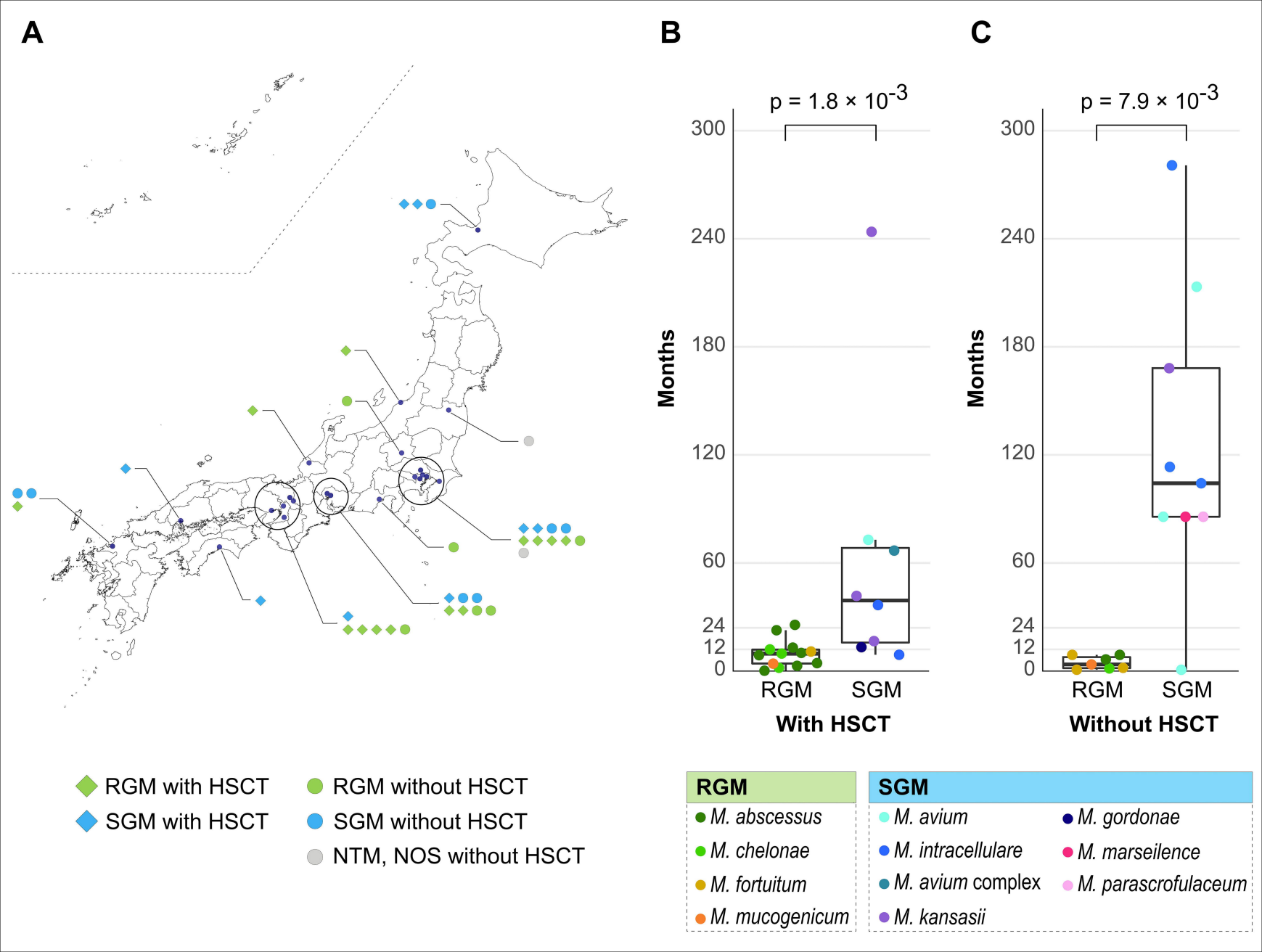
Abbreviations: HSCT, hematopoietic stem cell transplantation; NOS, not otherwise specified; RGM, rapid-growing mycobacteria; SGM, slow-growing mycobacteria.

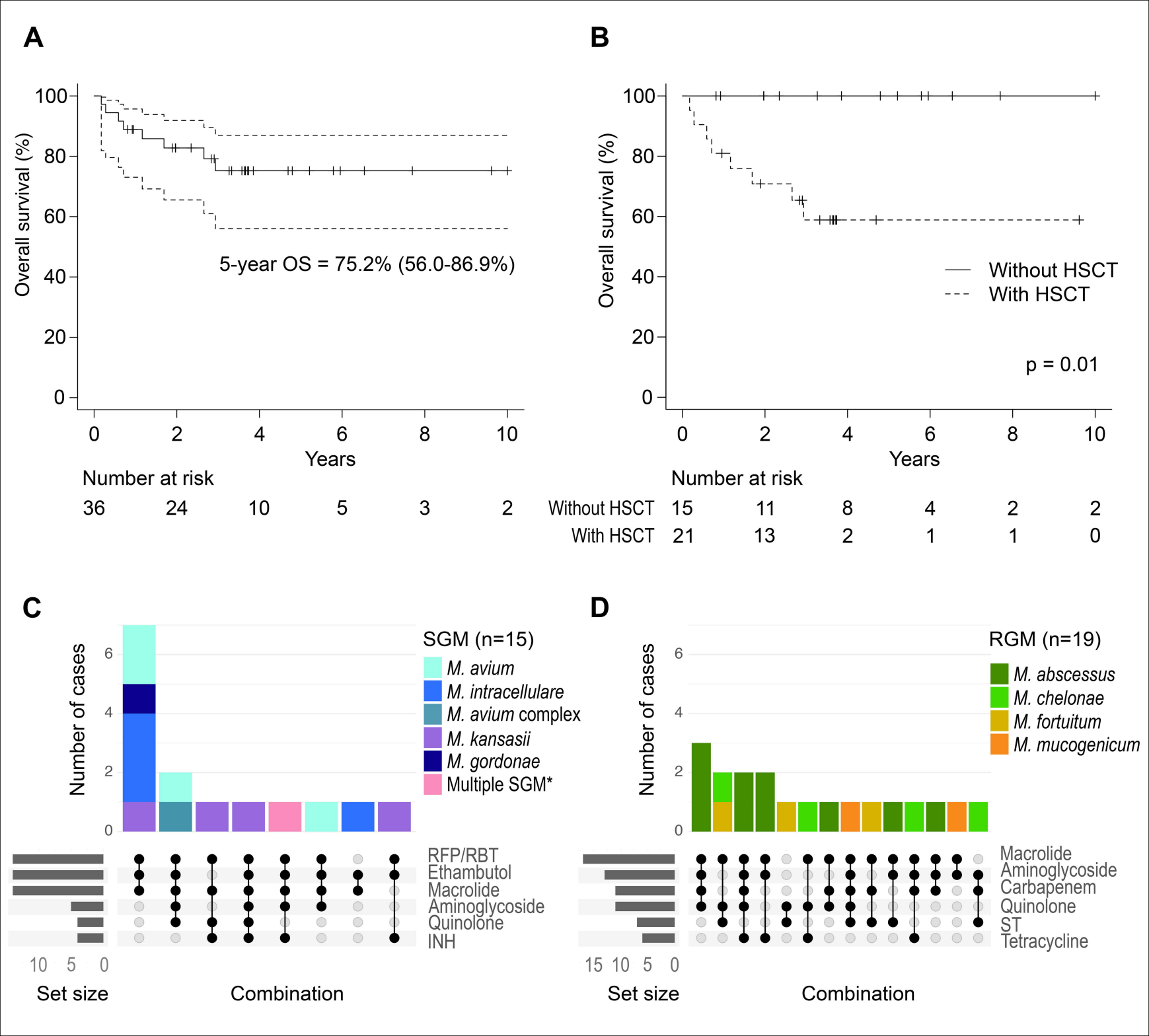
Figure 3. Clinical outcomes and the pattern of combinations of the top six chemotherapeutic agents used in the treatment of non-tuberculous mycobacterial (NTM) infections in pediatric hematology/oncology patients.

(A) Kaplan–Meier estimates of the overall survival (OS) rate in pediatric hematology/oncology patients with NTM infection. The 5-year OS rate for all patients was 75.2% [95% confidence interval (CI): 56–87] in the entire cohort. (B) Patients receiving hematopoietic stem cell transplantation (HSCT) had a 10-year OS rate of 59% (95% CI: 34–77, $p = 0.012$ by the log-rank test), whereas those who did not had no deaths from NTM infection. (C, D) The top six major antibiotic combinations used to treat NTM infection are summarized by UpSet plots. Panels C and D depict drug combinations used to treat slow-growing mycobacteria (SGM; n = 15) and rapid-growing mycobacteria (RGM; n = 19), respectively. Each colored bar represents a different NTM species. Color codes are displayed in the right column of each panel.

Abbreviations: INH, isoniazid; RBT, rifabutin; RFP, rifampicin; ST, sulfamethoxazole-trimethoprim.


With HSCT (n=21)
Without HSCT (n=15)
ALL
IEI
Others
Age, ≥ 6 years
Sex, male
Outpatient
Underlying structural lung damage
Outcome, death
Patient status
HSCT-NTM infection, > 100 days
Myeloablative conditioning
aGVHD, ≥ GradeII
cGVHD
Pulmonary GVHD
Other pulmonary complications
HSCT condition
Steroid exposure
Carcineurin inhibitor
Anti-thymocyte globulin
Other immunosuppressive agents
Cytotoxic chemotherapy
Agents
Disseminated
Pulmonary
Catheter related bloodstream
Bloodstream
Bone marrow
Skin/soft tissue
Joint
Infection sites
M. avium complex
M. kansasii
M. gordonae
M. parascrofulaceum
M. marseillense
M. abscessus
M. fortuitum
M. chelonae
M. mucogenicum
NTM, not otherwise specified
Mycobacterial species
UPN
12 13 24 30 10 01 26 37 02 15 06 16 31 19 05 35 33 04 36 11 22
14 07 25 08 03 18 29 20 21 32 34 23 17 28 27
ALL ALL AML ALL ALL AA ALL CGD ALL AML AA STAT1 GoF AML DBA ALL ALL IPEX GATA2 XLP-2 JMML ALL
ALL ALL ALL ALL ALL GATA2 HIES STAT2 GoF GATA2 NEMO NEMO HL Castlman EWS NB
HSCT condition
Severity of cGVHD
Extended
Limited
Agents
Steroid dosage
High, ≥ 1.0 mg/kg/day
Medium, ≥ 0.5, < 1.0 mg/kg
Low, < 0.5 mg/kg
ATG dosage
High, ≥ 2.5 mg/kg
Low, < 2.5 mg/kg
Infection sites
Diagnostic certainty
Definite
Probable
Only clinical diagnosis
Mycobacterial species
Slow growing mycobacteria
Rapid growing mycobacteria
NTM, not otherwise specified
Subspecies
M. avium complex
M. avium complex
M. avium
M. intracellulare
M. abscessus complex
M. massiliense (identified by WGS)
Secondary infection
Identified as pathogen during primary NTM treatment
Identified as pathogen after primary NTM treatment


A
B
C
p = 1.8 × 10-3
p = 7.9 × 10-3
Months
300
240
180
120
60
24
12
0
RGM
SGM
With HSCT
Without HSCT
RGM with HSCT
SGM with HSCT
RGM without HSCT
SGM without HSCT
NTM, NOS without HSCT
RGM
M. abscessus
M. chelonae
M. fortuitum
M. mucogenicum
SGM
M. avium
M. intracellulare
M. avium complex
M. kansasii
M. gordonae
M. marseilence
M. parascrofulaceum


A
Overall survival (%)
100
80
60
40
20
0
5-year OS = 75.2% (56.0-86.9%)
0
2
4
6
8
10
Years
Number at risk
36
24
10
5
3
2
B
Overall survival (%)
Without HSCT
With HSCT
p = 0.01
Years
Number at risk
Without HSCT 15 11 8 4 2 2
With HSCT 21 13 2 1 1 0
C
Number of cases
SGM (n=15)
M. avium
M. intracellulare
M. avium complex
M. kansasii
M. gordonae
Multiple SGM*
RFP/RBT
Ethambutol
Macrolide
Aminoglycoside
Quinolone
INH
Set size
Combination
D
Number of cases
RGM (n=19)
M. abscessus
M. chelonae
M. fortuitum
M. mucogenicum
Macrolide
Aminoglycoside
Carbapenem
Quinolone
ST
Tetracycline
Set size
Combination

Supplemental Data

Supplemental Methods **pp. 2**

Supplemental Tables **pp. 3–5**

Supplemental Table 1. **Details of the transplant setting and infection patterns for each hematopoietic stem cell transplant patient.**

Supplemental Table 2. **Estimated nontuberculous mycobacterial prevalence in the general pediatric population in Japan based on the Diagnosis and Procedure Combination database.**

Supplemental Figures **pp. 6–10**

Supplemental Figure 1. **Geographic distribution of institutions participating in this study.**

Supplemental Figure 2. **Number of newly diagnosed nontuberculous mycobacterial patients per year.**

Supplemental Figure 3. **Comparison of patient characteristics of RGM and SGM infections.**

Supplemental Figure 4. **Outcomes of nontuberculous mycobacterial infection in pediatric hematology/oncology patients.**

Supplemental Figure 5. **Combinations of chemotherapeutic agents used in treating nontuberculous mycobacterial infections in pediatric hematology/oncology patients.**

Supplemental Appendices **pp. 11–13**

Supplemental Appendix 1. **Participating institutions.**

Supplemental Appendix 2. **Patient data contributors.**

Supplemental Methods

Questionnaire

A detailed questionnaire on the clinical manifestations and demographic characteristics of NTM infection was administered, including age of onset, institutional diagnosis of primary disease, exposure to cytotoxic and/or immunosuppressive agents, transplantation outcomes, NTM antimicrobial agents, and survival outcomes. This questionnaire also included information on the NTM subspecies isolated. For patients with prior hematopoietic stem cell transplantation (HSCT), additional data on conditioning regimen, donor source, human leukocyte antigen identity, post-transplant immunosuppressive therapy, and transplant-related complications, particularly acute and chronic graft-versus-host disease (GVHD), were collected. The intensity of conditioning regimens for HSCT was classified as myeloablative and reduced intensity based on the definition of the Center for International Blood and Marrow Transplant Research (1).

Statistical methods and software libraries used for analysis and plotting

Statistical analyses were performed using EZR 1.55 (Saitama Medical Center, Jichi Medical University, Saitama, Japan) (2). Box and UpSet plots were created in Rstudio version 1.4.1103 using the packages “ggplot2” (https://ggplot2.tidyverse.org) and “ComplexUpset” (http://doi.org/10.5281/zenodo.3700590), respectively. The Wilcoxon rank-sum test was used to assess the difference between RGM and SGM at the time of infection, as noted in the box plot. For patients who underwent HSCT, the time to NTM onset was calculated from the date of transplantation. For IEI patients without HSCT, time to NTM onset was calculated from the date of birth, and for non-IEI patients without HSCT, including leukemia, time to NTM onset was calculated from the date of diagnosis of the underlying disease. All data analyses and plotting were performed using the statistical software package R Version 4.1.2, except for geographical analysis. The Python library "Geopandas" (https://github.com/geopandas/geopandas) was used to plot the geographic distribution.

References

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Supplemental Tables

Supplemental Table 1. Details of the transplant setting and infection patterns for each hematopoietic stem cell transplant patient.

UPN	Age at NTM onset, y	Primary disease	R/UR	HLA matching	Source	Intensity	Conditioning	TBI, Gy	ATG	GVHD prophylaxis	Type of NTM	Subspecies	Infection sites	Outcome
12	12.3	ALL	R*	8/8	BM	MAC	CY + ETP	12	-	CSA + MTX	SGM	*M. avium*	L	Alive
13	12.0	ALL	R	4/8	PBSC	RIC	FLU + MEL + AraC + ETP	-	+	TAC + MTX	SGM	*M. intracellulare*	L	Alive
24	5.0	AML	UR	5/6	CB	MAC	BU4 + MEL	-	-	CSA + steroid	SGM	*M. intracellulare*	L	Alive
30	9.7	ALL	UR	7/8	BM	MAC	MEL	12	-	TAC + MTX	SGM	*M. gordonae*	L	Alive
10	16.8	ALL	UR	6/8	CB	MAC	CY + ETP	12	-	TAC + MTX	RGM	*M. abscessus*	L, B	Dead
01	19.8	AA	UR	7/8	BM	RIC	FLU + MEL	3	+	TAC + MMF	RGM	*M. abscessus*	L	Alive
26	21.0	ALL	UR	6/8	BM	RIC	FLU + MEL + AraC	-	-	TAC + MTX	RGM	*M. abscessus*	L	Dead
37	18.3	CGD	UR	8/8	BM	RIC	FLU + BU2	3	+	TAC + MTX	RGM	*M. abscessus*	L	Dead
02	13.7	ALL	R	6/8	BM	MAC	BU4 + CLO	-	-	TAC + MTX	RGM	*M. fortuitum*	L	Alive
15	15.8	AML	UR	7/8	BM	MAC	BU4 + FLU + MEL	-	+	TAC + MTX	RGM	*M. abscessus*	L	Alive
06	14.5	AA	R*	5/8	BM	RIC	FLU + MEL	3	+	TAC + MTX + steroid	RGM	*M. abscessus*	L	Alive
16	4.3	STAT1 GoF	R*	8/8	BM	RIC	FLU + MEL	3	+	CSA + MTX	RGM	*M. abscessus*	L	Alive
31	3.7	AML	R	5/8	BM	RIC	FLU + MEL	-	-	TAC + MTX	RGM	*M. chelonae*	C	Dead
19	3.0	DBA	UR	8/8	BM	MAC	FLU + BU4	-	+	TAC+ MTX	RGM	*M. mucogenicum*	B	Alive
05	24.3	ALL	UR	6/8	BM	MAC	CY + ETP	12	-	CSA + MTX	SGM	*M. kansasii*	S	Dead
35	13.7	ALL	R	6/8	PBSC	MAC	CY	12	-	TAC + steroid	SGM	*M. kansasii*	S*	Dead
33	17.8	IPEX	UR	8/8	BM	RIC	FLU + MEL	4	+	TAC	RGM	*M. chelonae*	S	Alive
04	21.6	GATA2	UR	7/8	BM	RIC	FLU + MEL + ETP	3	+	CSA + MTX	RGM	*M. chelonae*	S	Dead
36	21.0	XLP-2	UR	8/8	BM	RIC	FLU + MEL + ETP	3	+	TAC + MTX	RGM	*M. abscessus*	S, C	Alive
11	11.9	JMML	R	5/8	PBSC	MAC	FLU + BU4 + MEL	-	-	TAC + MTX	SGM	*M. avium* complex	BM	Alive
22	17.3	ALL	UR	7/8	BM	MAC	CY + ETP	12	-	TAC + MTX	SGM	*M. kansasii*	J, M	Dead

Abbreviations: AA, aplastic anemia; ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; AraC, cytarabine; ATG, antithymocyte globulin; B, bloodstream; BM, bone marrow; BU2, reduced dose of busulfan; BU4, myeloablative dose of busulfan; C, catheter-related bloodstream; CB, cord blood; CGD, chronic granulomatous disease; CLO, clofarabine; CSA, cyclosporine; CY, cyclophosphamide; DBA, Diamond–Blackfan anemia; ETP, etoposide; FLU, fludarabine; GVHD, graft-versus-host disease; HLA, human leukocyte antigen; IPEX syndrome, immunodysregulation polyendocrinopathy enteropathy X-linked syndrome; J, joint; JMML, juvenile myelomonocytic leukemia; L, lung; M, muscle; MAC, myeloablative conditioning; MEL, melphalan; MMF, mycophenolate mofetil; MTX, methotrexate; NTM, nontuberculous mycobacterium; PBSC, peripheral blood stem cell; R, related donor; R*, sibling donor; RGM, rapid-growing mycobacteria; RIC, reduced intensity conditioning; S, skin; S*, subcutaneous insulin injection site; SGM, slow-growing mycobacteria; STAT1 GoF, *STAT1* gain-of-function mutation; TAC, tacrolimus; TBI, total body irradiation; UPN, unique patient number; UR, unrelated donor; XLP2, X-linked lymphoproliferative disease 2.

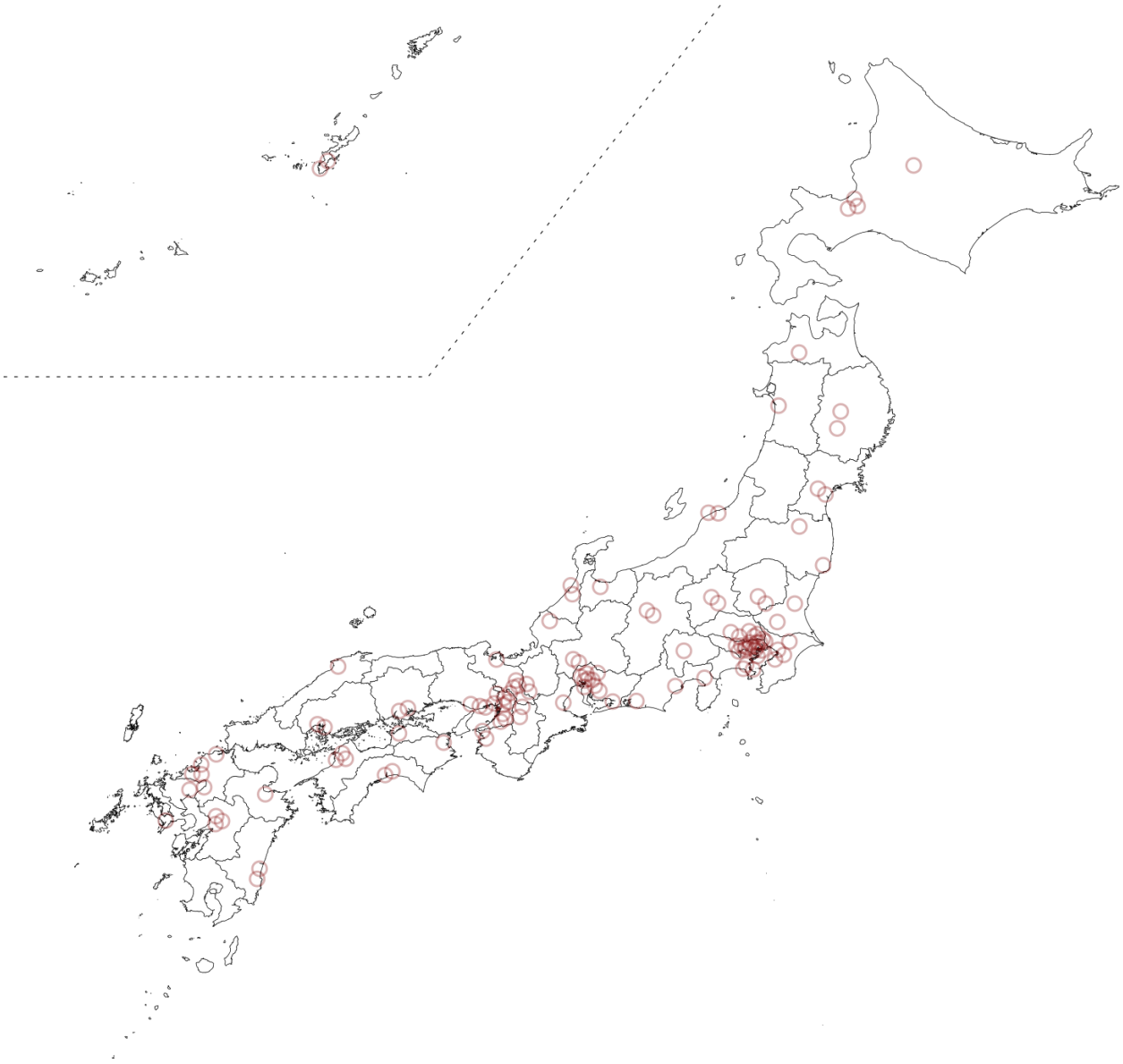
Supplemental Table 2. Estimated nontuberculous mycobacterial prevalence in the general pediatric population in Japan based on the Diagnosis and Procedure Combination database.

	Age group (years)	Study period (years)	Number of NTM cases	Denominator	Prevalence /100,000 inpatients)
General pediatric population	<20	April 2012–June 2022	5	Total number of pediatric inpatients (n = 741,962)	0.7

Because there are no epidemiological data on nontuberculous mycobacterial (NTM) infection in the general pediatric population in Japan, we estimated the prevalence using part of a nationwide inpatient administrative claims database called Diagnosis and Procedure Combination (DPC). DPC is a Ministry of Health, Labor and Welfare classification, introduced in 2002, to code the diagnosis and treatment of inpatients. It is linked to the healthcare subsidy system for hospitals, which benefit from revenue. Furthermore, most medium and large hospitals participate in this system. Our available regional DPC database covers over 90% of DPC hospitals in Aichi and Gifu prefectures, which comprise 7.6% of Japan's total population. We detected five distinct cases of NTM infection among hospitalized patients under 20 years of age between April 2012 and June 2022 in the database. We calculated the prevalence using the total number of hospitalized patients during the period as the denominator. Patients with NTM infection were identified if they had the NTM infection disease codes A310, A311, A318, A319, or B200 (International Classification of Diseases, 10th Revision) assigned to their principal diagnosis, most resource-intensive diagnosis, or diagnosis prompting hospitalization.

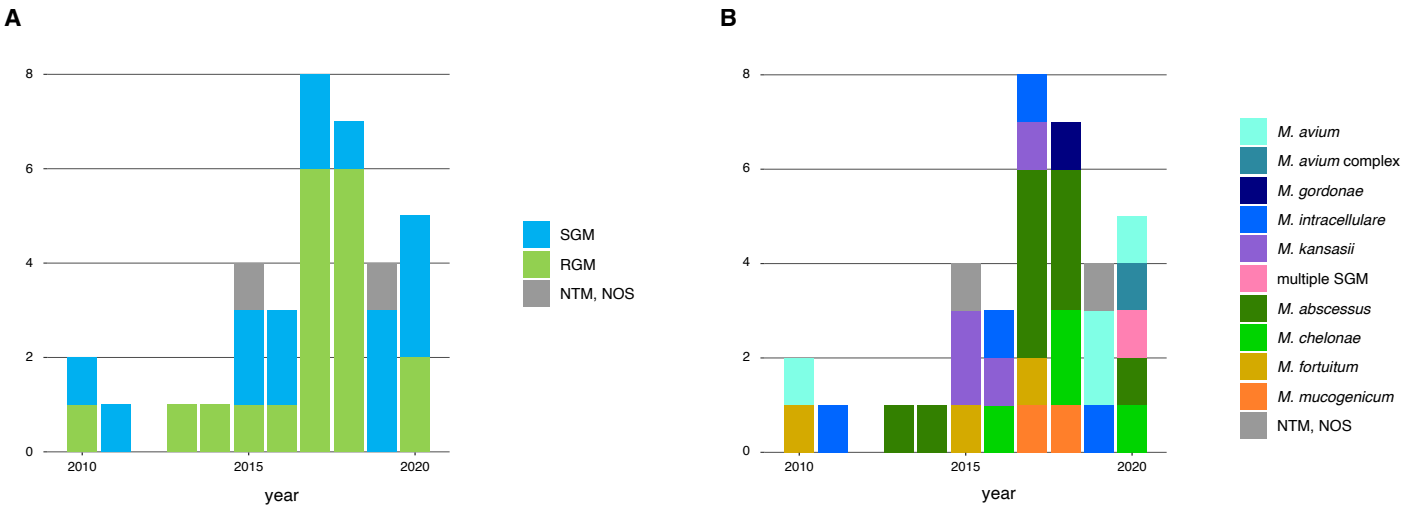
Supplemental Figures

Supplemental Figure 1. Geographic distribution of institutions participating in this study.



A total of 121 Japanese pediatric hematology/oncology institutions participated in this study. Red circles indicate the location of each participating institution.

Supplemental Figure 2. Number of newly diagnosed nontuberculous mycobacterial patients per year.

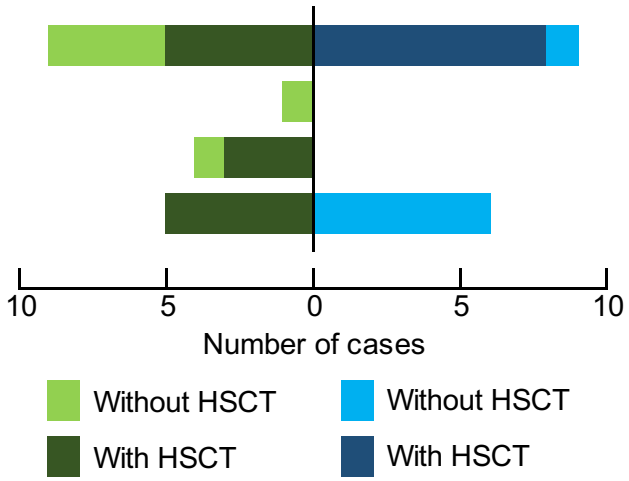


(A) Lime green bars, rapid-growing mycobacteria (RGM); light blue bars, slow-growing mycobacteria (SGM); gray bars, nontuberculous mycobacterial (NTM) not otherwise specified.

(B) Each colored bar indicates a different NTM species. Color codes are noted in the column to the right.

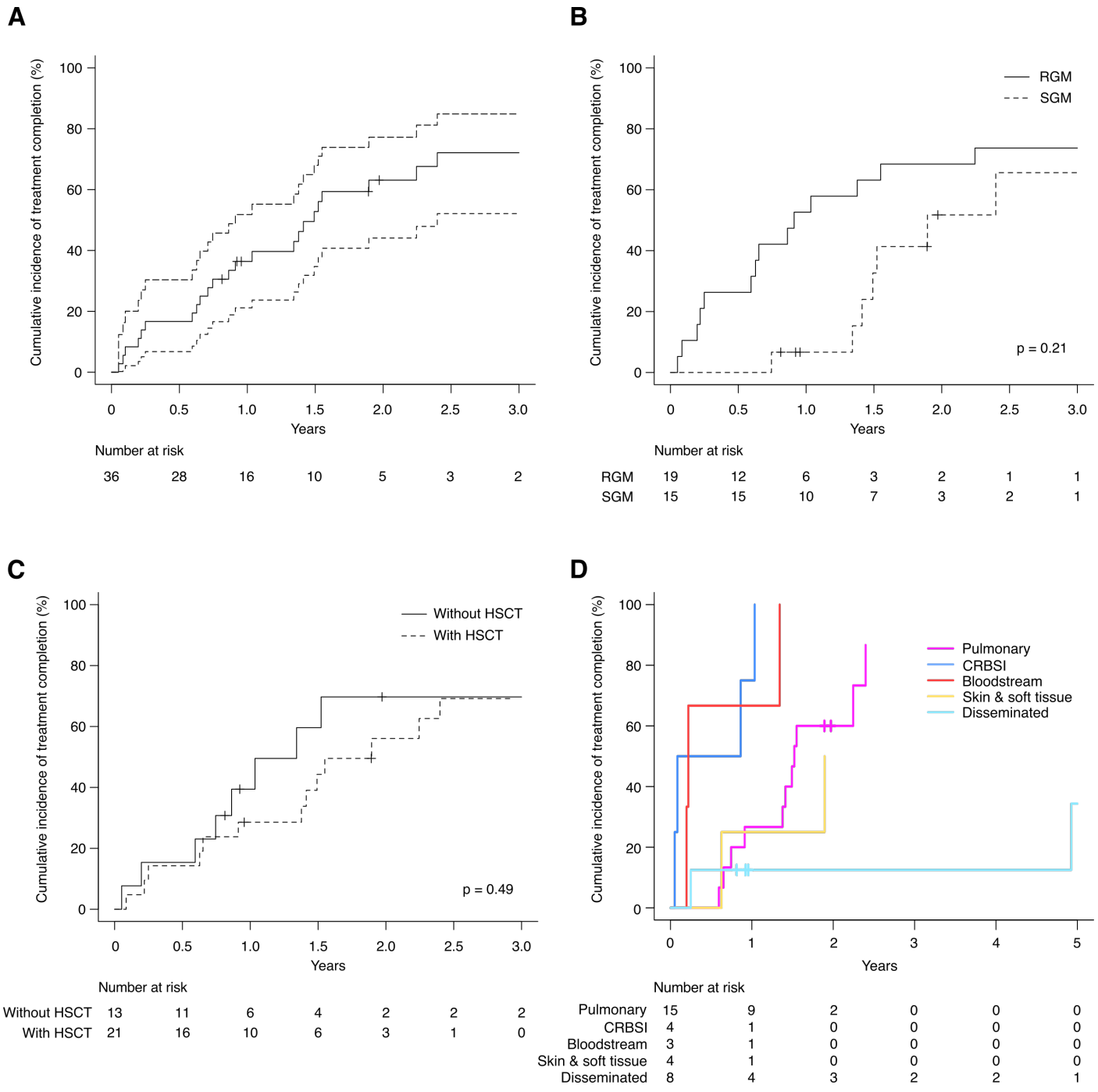
Supplemental Figure 3. Comparison of patient characteristics of RGM and SGM infections.

	RGM (n = 19)	SGM (n = 15)
Sex, male/female	8 / 11	9 / 6
Median age at NTM diagnosis, years (range)	14.6 (3.0–21.6)	12 (5.0–24.3)
Co-infecting pathogens with NTM, n (%)	4 (21)	1 (7)
Aspergillus species, n	3	-
Zygomycetes, n	1	-
S.epidermidis, n	-	1
Stem cell transplantation, n (%)	13 (68)	8 (53)
Primary diagnosis		
Hematologic malignancies		
Solid tumors		
Non-malignant hematological diseases		
Inborn error of immunity		



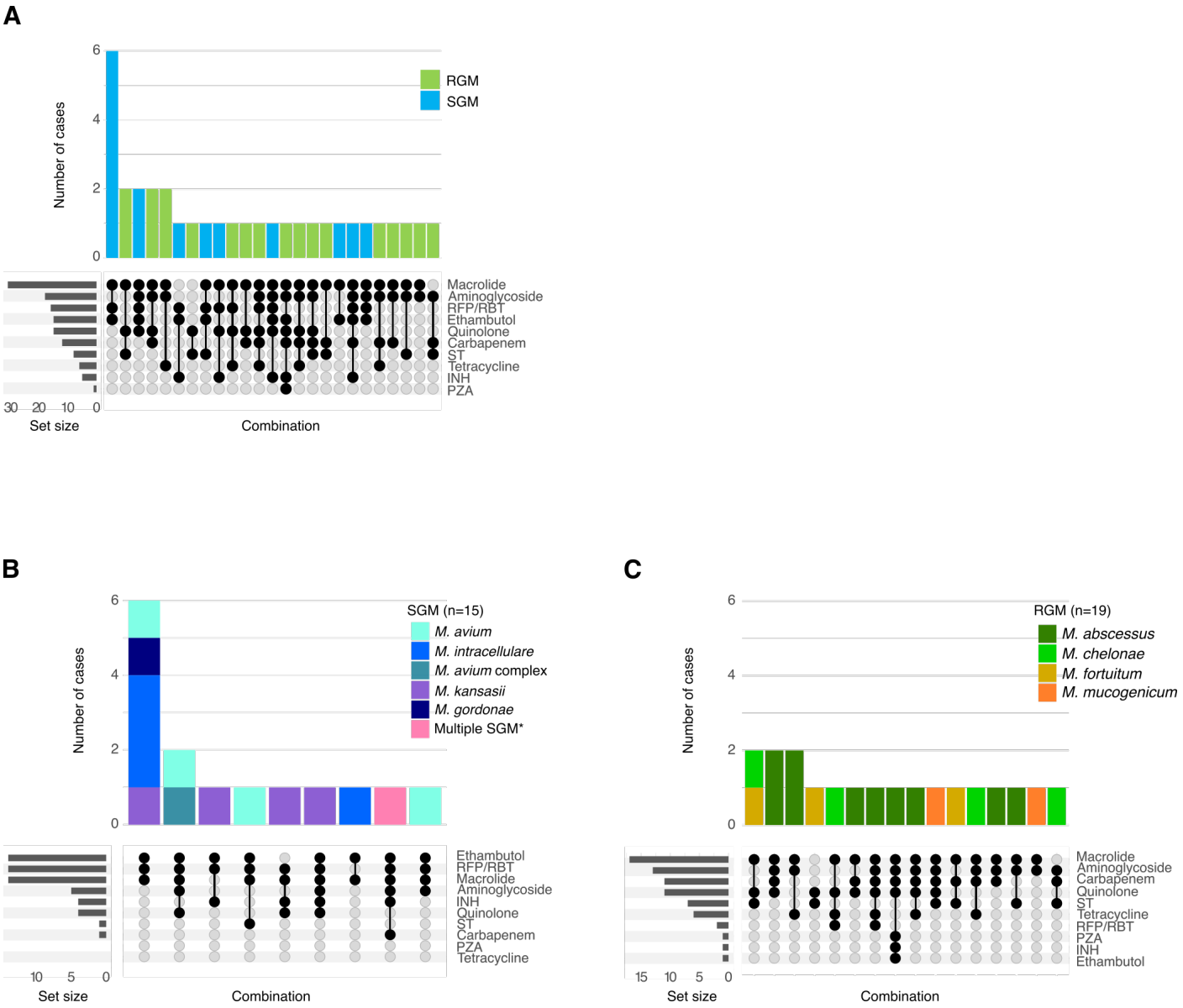
Green bars on the left indicate the number of rapid-growing mycobacterial (RGM) infections, and blue bars on the right indicate the number of slow-growing mycobacterial (SGM) infections. Light colors indicate cases without hematopoietic stem cell transplantation (HSCT), and dark colors indicate cases with HSCT. Patients were classified according to the type of nontuberculous mycobacterium (NTM) that first infected the patient.

Supplemental Figure 4. Outcomes of nontuberculous mycobacterial infection in pediatric hematology/oncology patients.



(A) Cumulative incidence of treatment completion in pediatric hematology/oncology patients with nontuberculous mycobacterial (NTM) infection. Cumulative incidence of treatment completion by: (B), classification of NTM growth rate; (C), presence of prior hematopoietic stem cell transplantation; (D), site of infection.
Abbreviations: CRBSI, catheter-related bloodstream infection; HSCT, hematopoietic stem cell transplantation; RGM, rapid-growing mycobacteria; SGM, slow-growing mycobacteria.

Supplemental Figure 5. Combinations of chemotherapeutic agents used in treating nontuberculous mycobacterial infections in pediatric hematology/oncology patients.



Antibiotic combinations used in treating nontuberculous mycobacterial (NTM) infections are summarized by UpSet plots. (A) Drug combinations used in the 34 pediatric hematology/oncology patients with identified NTM species. Lime green bars, rapid-growing mycobacteria (RGM); light blue bars, slow-growing mycobacteria (SGM). One case with unidentified NTM species was treated with three drugs (macrolide, aminoglycoside, and quinolone) and the other with two drugs (macrolide and quinolone) (data not shown). Panels B and C depict drug combinations used to treat slow-growing mycobacteria (SGM; n = 15) and rapid-growing mycobacteria (RGM; n = 19), respectively. Color codes are displayed in the right column of each panel.

Abbreviations: INH, isoniazid; PZA, pyrazinamide; RBT, rifabutin; RFP, rifampicin; ST, sulfamethoxazole-trimethoprim.

Supplemental Appendices

Supplemental Appendix 1. Participating institutions.

All of the following centers provide care for pediatric hematology/oncology patients and participated in this study: Aichi Medical University Hospital, Anjo Kosei Hospital, Asahikawa Medical University Hospital, Chiba Children's Hospital, Chiba University Hospital, Dokkyo Medical University Hospital, Ehime Prefectual Central Hospital, Ehime University Hospital, Fujita Health University Hospital, Fukuoka University Hospital, Fukushima Medical University Hospital, Gifu Municipal Hospital, Gifu University Hospital, Gunma Children's Medical Center, Gunma University Hospital, Hamamatsu University Hospital, Hirosaki University Hospital, Hiroshima Red Cross Hospital & Atomic-bomb Survivors Hospital, Hiroshima University Hospital, Hokkaido University Hospital, Hospital of the University of Occupational and Environmental Health , Hyogo Prefectural Amagasaki General Medical Center, Hyogo Prefectural Kobe Children's Hospital, Ibaraki Children's Hospital, Iwaki City Medical Center, Iwate Medical University Hospital, Iwate Prefectural Chubu Hospital, Japanese Red Cross Aichi Medical Center Nagoya Daiichi Hospital, Japanese Red Cross Aichi Medical Center Nagoya Daini Hospital, Japanese Red Cross Narita Hospital, Japanese Red Cross Otsu Hospital, Japanese Red Cross Wakayama Medical Center, Japanese Red Cross Wakayama Medical Center, Jichi Medical University Hospital, Juntendo University Hospital, Kanagawa Children's Medical Center, Kanazawa Medical University Hospital, Kanazawa University Hospital, Keio University Hospital, Kindai University Hospital, Kitano Hospital, The Tazuke Kofukai Medical Research Institute, Kobe City Nishi-Kobe Medical Center, Kobe University Hospital, Kochi Health Science Center, Kochi Medical School Hospital, Kumamoto Red Cross Hospital, Kumamoto University Hospital, Kurashiki Central Hospital, Kurume University Hospital, Kyorin University Hospital, Kyoto City Hospital, Kyoto University Hospital, Kyushu University Hospital, Matsuyama Red Cross Hospital, Mie University Hospital, Miyagi Children's Hospital, Miyazaki Prefectural Miyazaki Hospital, Nagano Children's Hospital, Nagasaki University Hospital, Nagoya City University Hospital, Nagoya Memorial Hospital, Nagoya University Hospital, Nakadori General Hospital, Nanbu Medical Center & Children's Medical Center, Nara City Hospital, Nara Medical University Hospital, National Center for Child Health and Development, National Center for Global Health and Medicine, National Defense Medical College Hospital, National Hospital Organization Kumamoto Medical Center, National Hospital Organization Kyushu Cancer Center, National Hospital Organization Maizuru Medical Center, National Hospital Organization Nagoya Medical Center, Nihon University Itabashi Hospital, Niigata Cancer Center Hospital, Niigata University Medical & Dental Hospital, Nippon Medical School Hospital, Oita University Hospital, Okayama University Hospital, Osaka City General Hospital, Osaka City University Hospital, Osaka Medical and Pharmaceutical University Hospital, Osaka University Hospital, Osaka Women's and Children's Hospital, Saga University Hospital, Saiseikai Yokohamashi Nanbu Hospital, Saitama Children's Medical Center, Saitama City Hospital, Saitama Medical University International Medical Center, Sapporo Hokuyu Hospital, Sapporo Medical University Hospital, Shiga University of Medical Science Hospital, Shikoku Medical Center for Children and Adults, Shimane University Hospital, Shinshu University Hospital, Shizuoka Cancer Center, Shizuoka Children's Hospital, St. Luke's International Hospital, St. Marianna University School of Medicine Hospital, Teikyo University Chiba Medical Center, Teikyo University Hospital, The Jikei University Hospital, The University of Tokyo Hospital, Toho University Omori Medical Center, Tohoku University Hospital, Tokai University Hospital, Tokushima University Hospital , Tokyo Medical And Dental University Medical Hospital, Tokyo Metropolitan Children's Medical Center, Toyama University Hospital, Toyohashi Municipal Hospital, Toyonaka Municipal Hospital, University Hospital, Kyoto Prefectural University of Medicine, University of Fukui Hospital, University of Miyazaki Hospital, University of the Ryukyu Hospital,

University of Tsukuba Hospital, University of Yamanashi Hospital, Wakayama Medical University Hospital, Yokohama City University Hospital.

Supplemental Appendix 2. Patient data contributors.

The following is a complete list of investigators who contributed by providing detailed patients data: Haruna Okuno, Gunma University Hospital; Makiko Mori, Yuichi Mitani, and Takuma Ohnishi, Saitama Children's Medical Center; Nao Yoshida, Japanese Red Cross Aichi Medical Center Nagoya Daiichi Hospital; Shinya Osone, University Hospital, Kyoto Prefectural University of Medicine; Toshihiro Matsui, National Center for Child Health and Development; Chihaya Imai, Niigata University Medical & Dental Hospital; Hideki Sano, Fukushima Medical University Hospital; Hiroaki Kikuchi, Kochi Medical School Hospital; Hiroshi Yagasaki, Nihon University Itabashi Hospital; Katsutsugu Umeda, Kyoto University Hospital; Koji Suzuki, University of Fukui Hospital; Motohiro Matsui, Tokyo Metropolitan Children’s Medical Center; Naoki Sakata, Kindai University Hospital; Naoto Fujita, Hiroshima Red Cross Hospital & Atomic-bomb Survivors Hospital; Nobuyuki Yamamoto, Kobe University Hospital; Takako Miyamura, Osaka University Hospital; Takayuki Takachi, Shizuoka Children’s Hospital; Yuichi Taneyama, Chiba Children’s Hospital; Aiko Kozaki, Hyogo Prefectural Kobe Children's Hospital; Kimiyoshi Sakaguchi, Hamamatsu University Hospital.