Journal of Clinical Immunology (2025) 45:90
https://doi.org/10.1007/s10875-025-01869-z

RESEARCH

Quality of Life in Japanese Patients with Primary Immunodeficiency Disease is Disrupted throughout the Year

Toshinao Kawai[1] · Hirokazu Kanegane[2] · Masataka Ishimura[3] · Satoshi Okada[4] · Nobuaki Okamatsu[5] · Kaori Nakagawa[5] · Madoka Go[6] · Shinichi Noto[7]

Received: 13 June 2024 / Accepted: 1 February 2025

Abstract

Patients with primary immunodeficiency disease (PID) have an increased susceptibility to infection and may experience negative impacts on health-related quality of life (HR-QOL) and activities of daily living. This prospective observational study of patients aged≥12 years with PID assessed HR-QOL, work impairment, and disease-related daily burden over a full year, with a focus on seasonal variation. The study period was from October 2021 to November 2023. Data were collected using an online system. HR-QOL was assessed using EuroQol-5 Dimensions-5 Levels (EQ-5D-5L) and the Medical Outcomes Study 36-Item Short Form Health Survey (SF-36), work impairment with the Work Productivity and Activity Impairment (WPAI) questionnaire, and disease-related burden with a questionnaire designed for this study. In patients with PID (N=56) and healthy volunteers (N=43), no significant seasonal variation was observed in EQ-5D-5L, SF-36, or WPAI scores. With few exceptions, patients with PID had significantly lower EQ-5D-5L, SF-36, and WPAI scores than healthy volunteers in all seasons. In patients with PID, disease-related symptoms and limitations of daily living persisted throughout the year, regardless of season. In conclusion, patients with PID had lower quality of life and were more socially, physically, and mentally stressed in all seasons compared with healthy individuals.

Keywords 36-item Short Form Health Survey · Activities of daily living · Health-related quality of life · Patient reported outcome measures · Work Productivity and Activity Impairment (WPAI) questionnaire

Introduction

Primary immunodeficiency disease (PID), also referred to as inborn errors of immunity, collectively refers to over 500 heterogeneous inherited genetic disorders characterized by impairment of the immune system [1–3]. Patients with PID characteristically exhibit an increased severity or frequency of infections and/or increased susceptibility to autoimmunity, autoinflammatory diseases, allergies, and/or malignancy [1–3], all of which often require long-term treatment. Common supportive treatments for PID include immunoglobulin replacement therapy, and prophylactic antibiotics and antifungals throughout the year [4, 5]. Symptoms and complications of PID, the burden of long-term treatments, and adverse events from treatments may result in negative impacts on health-related quality of life (HR-QOL) and activities of daily living in patients with PID [6–9].

In Japan, PID has an estimated prevalence rate of 2.2–2.3 per 100,000 individuals [10, 11], is designated as an intractable disease, and is listed in the public assistance program.

✉ Hirokazu Kanegane
hkanegane.ped@tmd.ac.jp

1 Division of Immunology, National Center for Child Health and Development, Tokyo, Japan

2 Department of Child Health and Development, Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental University (TMDU)/Institute of Science Tokyo, 1-5-45 Yushima, Bunkyo-ku, Tokyo 113-8510, Japan

3 Department of Pediatrics, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan

4 Department of Pediatrics, Graduate School of Biomedical and Health Sciences, Hiroshima University, Hiroshima, Japan

5 Medical Franchise RD, Japan Medical Office, Takeda Pharmaceutical Company Limited, Tokyo, Japan

6 Rare Disease, Evidence Generation & Outcomes Research, Japan Medical Office, Takeda Pharmaceutical Company Limited, Tokyo, Japan

7 Department of Rehabilitation, Niigata University of Health and Welfare, Niigata, Japan

Published online: 07 May 2025

The results of a 2017 survey suggest that susceptibility to infection, treatment-related burden, and negative impacts on daily living, schooling, and working are experienced by many patients with PID in Japan [12]. While the 2017 survey provided important insights into the lives of patients with PID in Japan, it was not a longitudinal study and did not use validated instruments for assessing HR-QOL. In addition, given that increased susceptibility to infection is a characteristic of PID, changes in seasons may have an impact owing to the seasonality of many infectious diseases [13–15]. All islands of Japan experience four distinct seasons, although the northern islands have a subarctic climate, while the southern islands have a subtropical climate [16]. It is expected that seasonal variation may have an impact on disease symptoms, treatment burden, daily activity, work performance (including absenteeism), and overall HR-QOL. Further insights into the HR-QOL of patients with PID may therefore be gained from studies designed to assess the effect of seasonal variation.

The objective of this prospective observational study of patients with PID in Japan was to assess HR-QOL, work impairment, and disease-related daily burden over a full year, with a focus on seasonal variation. The baseline results from this study have been reported previously in an interim analysis [17].

Materials and Methods

Study Design

This was a prospective, non-interventional observational study of patients with PID conducted in Japan between October 2021 and November 2023. This report includes data collected up to May 6, 2023. Patients with PID and healthy volunteers were enrolled between November 2021 and May 2022 and were observed over a one-year period. Data were collected using an online electronic patient-reported outcomes data system (3H P-Guardian, developed by 3H Clinical Trial Inc., Tokyo, Japan); study site visits were not required by the participants. Participants aged ≥16 years answered the HR-QOL and limitations of daily living questions four times in total, once every season; these participants also recorded disease-related symptoms once per week. Participants aged≥12 to <16 years completed the study after answering the HR-QOL and limitations of daily living questions only once. The study was conducted in accordance with ethical principles that have their origin in the Declaration of Helsinki, the Ethical Guidelines for Medical and Biological Research Involving Human Subjects (issued by the Japanese Ministry of Education, Culture, Sports, Science and Technology/Ministry of Health, Labour and Welfare/Ministry of Economy, Trade and Industry on March 23, 2021), and all other applicable laws and regulations, including laws on data privacy and guidelines/regulations on conflicts of interest. The protocol, informed consent form, and study questionnaires were approved by the Ethics Committee of the Japan Conference of Clinical Research (a non-profit organization). The study was registered at the University hospital Medical Information Network clinical trials registry (ID: UMIN000045622). Written informed consent was provided online by all participants or their legal representative. The study design has been described in detail previously for the interim analysis [17].

Study Population

The study population included patients with PID and healthy volunteers aged ≥12 years, who resided in Japan and possessed a smartphone [17]. Patients with PID included in this study had a diagnosis of PID and were registered at or referred from a non-profit patient association (PID Tsubasa-No-Kai; npo-pidtsubasa.org), or were referred by a physician affiliated with the Japanese Society for Immunodeficiency and Autoinflammatory Diseases. Patients with PID were excluded from the study if they had a diagnosis of an inherited autoinflammatory disease, such as familial Mediterranean fever. Healthy volunteers were excluded from the study if they had any of the following: (i) type 2 diabetes, hypertension, dyslipidemia, liver disease, renal disease, thyroid disease, cardiac disease, adrenal disease, any other metabolic disorder, or any mental disease (e.g., depression); (ii) any physical symptoms that interfered with daily activities; (iii) regular medication use or clinic visits for any disease (except for seasonal allergic diseases); (iv) a history of any severe medical conditions; (v) a drug or food allergy; or (vi) a family history of PID.

Endpoints and Outcome Measures

The endpoints of this study were as follows: (i) HR-QOL of patients with PID in each season, as assessed using the EuroQol-5 Dimensions-5 Levels (EQ-5D-5L) and the Medical Outcomes Study 36-Item Short Form Health Survey (SF-36) (primary endpoint); (ii) comparison of HR-QOL in patients with PID and healthy volunteers in each season (assessed using EQ-5D-5L and SF-36); (iii) work productivity in patients with PID in each season, as assessed using the Work Productivity and Activity Impairment (WPAI) questionnaire; (iv) comparison of work productivity in patients with PID and healthy volunteers in each season (assessed using WPAI); and (v) limitations of daily activities in patients with PID in each season. The four seasons were defined as follows, according to terminology provided

by the Japan Meteorological Agency: spring as March 1 to May 31, summer as June 1 to August 31, autumn as September 1 to November 30, and winter as December 1 to February 28.

The validated Japanese versions of the EQ-5D-5L [18] and SF-36 [19], and the certified Japanese version of the WPAI questionnaire (General Health version 2.0) [20], were used in this study. EQ-5D-5L measures HR-QOL in five dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) and overall health rated by the respondents on a 0–100 visual analog scale (VAS) [21]. SF-36 assesses eight health concepts (physical functioning, bodily pain, role limitations due to physical health problems, role limitations due to personal or emotional problems, emotional well-being, social functioning, energy/fatigue, and general health perceptions), which are collated into summary scores [22]; here we report the two-component scores Physical Component Summary (PCS) and Mental Component Summary (MCS). For this study, SF-36 items were answered by the participants in reference to their status in the previous 4 weeks. The WPAI assesses absenteeism, presenteeism, total work productivity impairment (absenteeism plus presenteeism), and total activity impairment outside of the workplace, in employed participants only [20].

Daily living limitations in patients with PID were assessed using a questionnaire developed for this study [17]. The questionnaire included questions assessing limitations of daily living within the past 3 months related to infections/symptoms, treatments, and prevention of infections/symptoms.

Statistical Analysis

To optimize study feasibility, the planned sample size was 150 patients with PID, with 50 healthy volunteers recruited during enrollment [17]. The full analysis set (FAS) was defined as enrolled participants who completed the HR-QOL questionnaire at least once. The per protocol set (PPS) excluded patients with PID who only answered one or two of the PID disease–related questions about daily living limitations, prevention of symptoms, and disease symptoms, and healthy volunteers who responded to HR-QOL questions but could not be judged as being healthy at the time of the questionnaire. The PPS for seasonal response analysis (PPS-1) excluded participants in the PPS who were aged < 16 years or had allogenic hematopoietic cell transplantation as the treatment modality. The PPS with complete responses to seasonal questions (PPS-2) included participants in the PPS-1 who responded to all four seasonal response items. Other than demographic data, the analyses presented in this article are for the PPS-2 dataset only.

HR-QOL (EQ-5D-5L and SF-36) and WPAI scores were summarized for patients with PID and healthy volunteers in each season (spring, summer, autumn, winter). In each season, SF-36 scores (PCS, MCS, and subscales), EQ-5D-5L scores (VAS and total), and WPAI scores were compared between patients with PID and healthy volunteers using unpaired t-tests or the Mann-Whitney U test for comparison between two groups. Variations in WPAI scores between groups (patients with PID vs. healthy volunteers) and between seasons (spring, summer, autumn, winter) were assessed using a repeated measures two-way analysis of variance (ANOVA), with WPAI scores as the dependent variable and group, season, and group–season interaction as fixed effects. Data on disease symptoms and limitations of daily living in each season were aggregated and tabulated.

All statistical tests were conducted at a two-sided significance level of 0.05. All analyses were conducted using SAS 9.4 or higher (SAS Institute Inc., Cary, NC, USA).

Results

Participants

The FAS included 71 patients with PID and 47 healthy volunteers, and the PPS included 71 patients with PID and 45 healthy volunteers (Fig. 1). The PPS-1 comprised 59 patients with PID and 45 healthy volunteers, and the PPS-2 comprised 56 patients with PID and 43 healthy volunteers. Just under half of the patients with PID in the PPS-2 (48.2%) and all of the healthy volunteers (100%) were recruited in 2022.

Demographic and Baseline Clinical Characteristics

Similar demographic characteristics were seen in the PPS-1 and PPS-2 (Table 1). Patients with PID were predominantly male (59.3% and 60.7% of the PPS-1 and PPS-2, respectively), as were healthy volunteers (64.4% and 62.8% of the PPS-1 and PPS-2, respectively). The mean (standard deviation [SD]) age of patients with PID was 37.9 (12.2) and 38.1 (11.8) years in the PPS-1 and PPS-2, respectively. Although the age for enrollment was set as ≥12 years, no healthy volunteers aged ≥12 to <16 years enrolled in this study. Healthy volunteers had a mean (SD) age of 35.0 (11.8) and 35.4 (11.8) years in the PPS-1 and PPS-2, respectively. The age distributions of patients with PID and healthy volunteers in the PPS-1 and PPS-2 were similar.

Patients with PID were most commonly classified as having “predominantly antibody deficiencies” in the International Union of Immunological Societies (IUIS) classifications (61.0% and 64.3% of PPS-1 and PPS-2, respectively; Table 1). The next most common IUIS classifications were

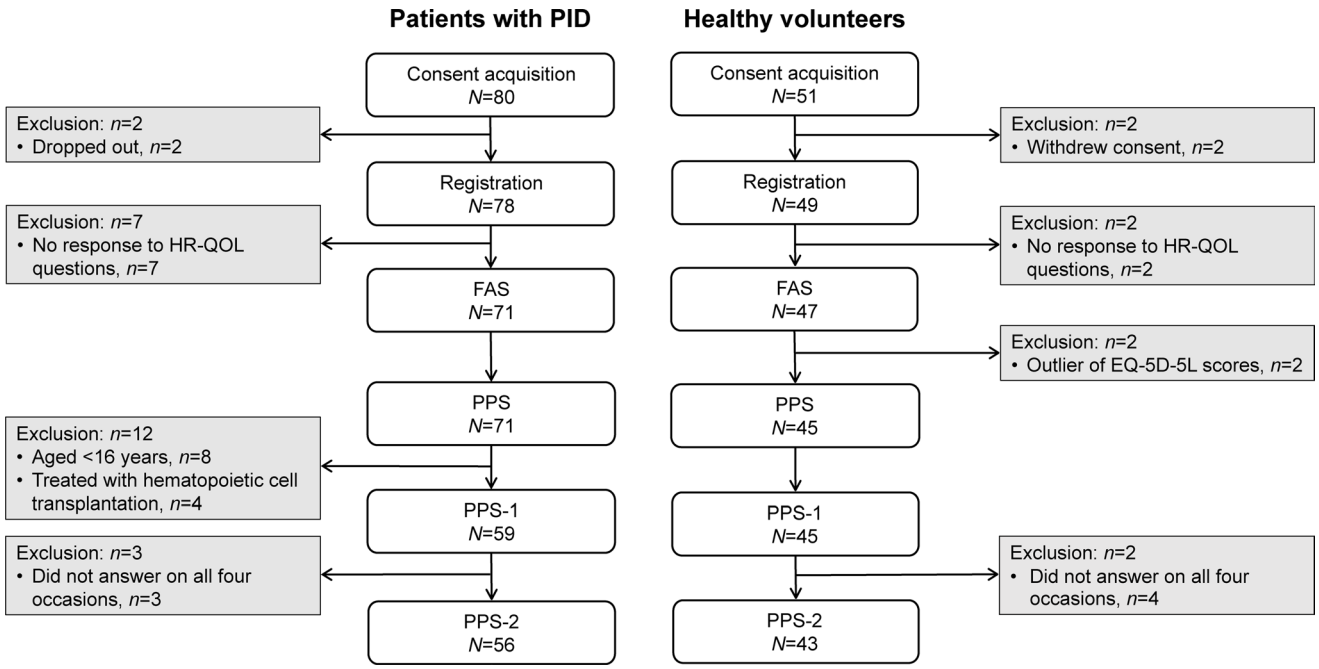

Fig. 1 Flow chart of research participants. EQ-5D-5L, EuroQol-5 Dimensions-5 Levels; FAS, full analysis set; HR-QOL, health-related quality of life; PID, primary immunodeficiency; PPS-1, per protocol set for seasonal response analysis; PPS-2, per protocol set with complete responses to seasonal questions

"combined immunodeficiencies with associated or syndromic features" (18.6% and 17.9% of PPS-1 and PPS-2, respectively) and "congenital defects of phagocyte number and function" (10.2% and 10.7% of PPS-1 and PPS-2, respectively).

Treatments received by patients with PID in the PPS-1 were subcutaneous immunoglobulin replacement therapy (45.8%), oral antibiotics (42.4%), intravenous immunoglobulin replacement therapy (28.8%), oral antifungals (25.4%), topical steroids (18.6%), immunosuppressants (13.6%), oral steroids (11.9%), antiviral agents (5.1%), and other (6.8%).

Seasonal Variation in HR-QOL

In the PPS-2, for both EQ-5D-5L and SF-36, no seasonal variation was observed in patients with PID or healthy volunteers (Fig. 2). Patients with PID had significantly lower SF-36 PCS and MCS scores compared with healthy volunteers in all seasons ($P<0.001$, unpaired t-test; Fig. 2a and b). Similar results were observed for SF-36 subscale scores (Online Resource, Fig. S1). An exception was the SF-36 mental health subscale, in which scores were significantly lower in patients with PID than in healthy volunteers only in summer ($P=0.031$, unpaired t-test; Online Resource, Fig. S1h). Patients with PID had significantly lower EQ-5D-5L VAS and total scores compared with healthy volunteers (VAS $P<0.01$, total score $P<0.001$, unpaired t-tests), except for the EQ-5D-5L VAS score in spring ($P=0.084$, unpaired t-test; Fig. 2c and d).

Seasonal Variation in WPAI

Patients with PID generally showed significantly greater absenteeism, presenteeism, work productivity loss, and activity impairment compared with healthy volunteers ($P<0.05$, Mann-Whitney U test; Fig. 3). The only exceptions were absenteeism and presenteeism in winter, which were not significantly different between the two groups (Fig. 3a and b). For all four WPAI scores, there was no significant effect of season and no participant group (patients with PID/healthy volunteers)–season interaction effect (ANOVA analysis).

Seasonal Variation in PID Disease–Related Symptoms

No consistent pattern of seasonal variation was observed in any PID disease–related symptoms (Online Resource, Table S1). PID disease–related symptoms that occurred in >50% of patients with PID included changes in condition, malaise (fatigue), headache, nasal discharge, cough and phlegm (except for summer), sore throat and nasal congestion (winter only), and skin itching (except for spring) (Table S1). Among healthy volunteers, only changes in condition occurred in >50% of people.

Table 1 Demographic characteristics of participants (PPS-1 and PPS-2)

Variable	PPS-1		PPS-2	
	Patients with PID (*N*=59)	Healthy volunteers (*N*=45)	Patients with PID (*N*=56)	Healthy volunteers (*N*=43)
Male sex, *n* (%)	35 (59.3)	29 (64.4)	34 (60.7)	27 (62.8)
Mean age in years (SD)	37.9 (12.2)	35.0 (11.8)	38.1 (11.8)	35.4 (11.8)
Age group, *n* (%)				
16–20 years	4 (6.8)	7 (15.6)	3 (5.4)	6 (14.0)
21–29 years	12 (20.3)	8 (17.8)	11 (19.6)	8 (18.6)
30–39 years	15 (25.4)	15 (33.3)	15 (26.8)	14 (32.6)
40–49 years	17 (28.8)	9 (20.0)	17 (30.4)	9 (20.9)
50–59 years	9 (15.3)	4 (8.9)	8 (14.3)	4 (9.3)
≥60 years	2 (3.4)	2 (4.4)	2 (3.6)	2 (4.7)
IUIS classification, *n* (%)				
Combined immunodeficiency syndrome	4 (6.8)	–	3 (5.4)	–
Combined immunodeficiencies with associated syndromic features	11 (18.6)	–	10 (17.9)	–
Predominantly antibody deficiencies	36 (61.0)	–	36 (64.3)	–
Immunomodulatory disorders	2 (3.4)	–	1 (1.8)	–
Congenital defects of phagocyte number and function	6 (10.2)	–	6 (10.7)	–
Abnormalities of innate immunity	0	–	0	–
Complement deficient	0	–	0	–
Diseases with a primary immunodeficiency phenotype	0	–	0	–

Abbreviations: IUIS, International Union of Immunological Societies; PID, primary immunodeficiency; PPS-1, per protocol set for seasonal response analysis; PPS-2, per protocol set with complete responses to seasonal questions; SD, standard deviation

Limitations of Daily Living Related to PID Symptoms

More than half of patients with PID assessed "susceptibility to infection" as a limitation to their daily living (58.9–71.4%; Fig. 4). The next most commonly reported limitation was "difficult-to-cure infections" (48.2–55.4%). Although numerically higher percentages of patients reporting "susceptibility to infection" as a limitation were observed during summer and autumn, there was not a strong seasonal variation signal in any of the limitations of daily living.

When patients were asked about limitations of daily living with respect to prevention of PID symptoms, the most commonly reported (>60% of patients) were "wear a mask when going out" (78.6–92.1%), "avoid crowds as much as possible" (71.4–82.1%), and "wash hands and gargle carefully and frequently to avoid infection" (67.9–71.4%; Fig. 5). As with the other daily living limitations, limitations relating to prevention of symptoms did not show any strong seasonal variation.

Discussion

This analysis of a one-year prospective observational study provides the first comprehensive seasonal analysis of HR-QOL, workplace impairment, and disease-related burdens in daily life in patients with PID in Japan. Symptoms of PID persisted throughout the year, regardless of the season, and patients with PID reported poorer HR-QOL and greater workplace impairment than healthy people throughout the year. In addition, patients with PID experienced substantial burdens in daily life in every season.

It was expected that patients with PID would be more susceptible to infectious diseases in winter, similar to the general healthy population. With respect to disease symptoms, while there was no overall seasonal pattern observed, the percentage of patients experiencing sore throat and nasal congestion was >50% only in the winter, and cough and phlegm were experienced by <50% of patients in summer. While more than half of patients with PID reported susceptibility to infection and difficult-to-cure infections as limitations of their daily living, the highest percentages of patients reporting this limitation were seen in summer and autumn, rather than in winter. The daily limitations related to the potential of an infection becoming serious and being susceptible to infections that healthy people do not get were also reported by more than a third of patients with PID. The percentage of patients who reported these limitations of daily living was reasonably consistent across the seasons, which suggests that patients with PID are aware of their risk of infection, including from opportunistic infectious diseases, throughout the year. An awareness of risk of infection is consistent with the majority of patients with PID in this study reporting recurrent respiratory infections [17]. Also consistent with this interpretation, patients with PID did not show large variations in their symptom prevention behaviors across the year, although there was a slight increase in the percentage of patients wearing a mask when going out and avoiding crowds in winter.

Given this study did not reveal any clear seasonal patterns in disease symptoms or disease burden, it is perhaps unsurprising that patients with PID did not show any seasonal variation in HR-QOL or work productivity. However, it was clear that patients with PID had lower HR-QOL than healthy volunteers throughout the year. This pattern was

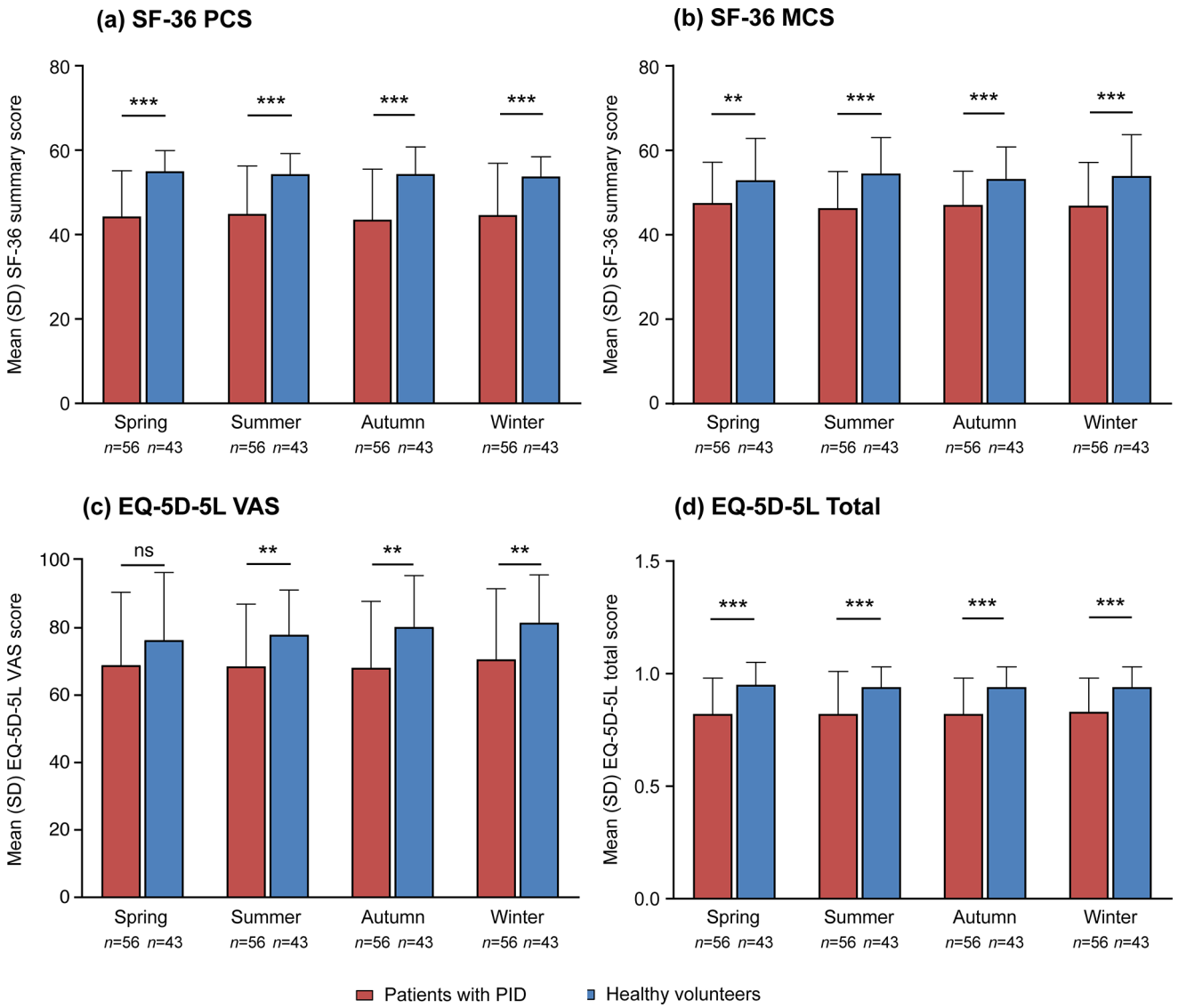

Fig. 2 Seasonal variation of HR-QOL in patients with PID and healthy volunteers (PPS-2). (**a**) SF-36 PCS score; (**b**) SF-36 MCS score; (**c**) EQ-5D-5L VAS score; (**d**) EQ-5D-5L total score. ** $P<0.01$, *** $P<0.001$ (unpaired t-test). Error bars indicate SD. Spring was defined as March 1 to May 31, summer as June 1 to August 31, autumn as September 1 to November 30, and winter as December 1 to February 28. EQ-5D-5L, EuroQol-5 Dimensions-5 Levels; HR-QOL, health-related quality of life; MCS, Mental Component Summary (two-component model); ns, non-significant; PCS, Physical Component Summary (two-component model); PID, primary immunodeficiency; PPS-2, per protocol set with complete responses to seasonal questions; SD, standard deviation; SF-36, Medical Outcomes Study 36-Item Short Form Health Survey; VAS, visual analog scale

seen in the scores of both of the validated HR-QOL instruments used (SF-36 and EQ-5D-5L). These results are consistent with previous reports of lower HR-QOL in patients with PID than in healthy people [7–9], and of HR-QOL of patients with PID being lower than population norms [6]. Employed patients with PID also had significantly greater absenteeism, presenteeism, work productivity loss, and activity impairment compared with healthy volunteers in every season, without significant seasonal change.

The reasons for the lack of the expected seasonal variation in disease symptoms, HR-QOL, and work productivity of patients with PID are unclear. It is possible that differences in regional climates (from subarctic to subtropical) may have had some impact on seasonal infection patterns, illness, and even work productivity. Despite these regional climate differences in Japan, one possibility is that the ongoing COVID-19 pandemic disrupted normal seasonal variation in both infectious disease risk and infection control behaviors, including wearing masks and limitations on working in person, which may have affected both patients with PID and healthy volunteers. It has been reported that in the early stages of the pandemic, public health measures

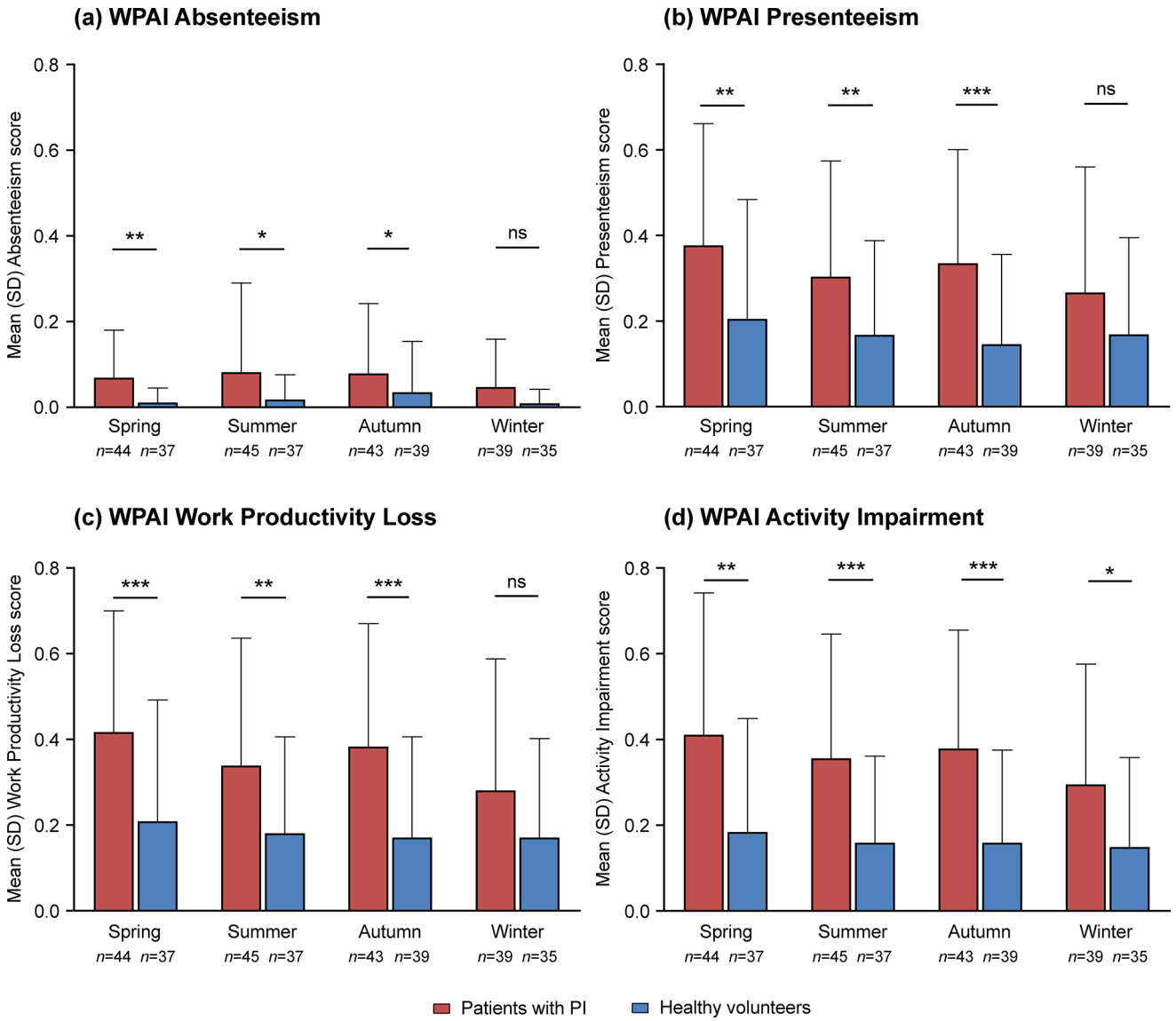

Fig. 3 Seasonal variation of WPAI scores in patients with PID and healthy volunteers (employed participants within PPS-2). (**a**) Absenteeism; (**b**) Presenteeism; (**c**) Work Productivity Loss; (**d**) Activity Impairment. * $P<0.05$, ** $P<0.01$, *** $P<0.001$ (Mann-Whitney U test). Error bars indicate SD. Spring was defined as March 1 to May 31, summer as June 1 to August 31, autumn as September 1 to November 30, and winter as December 1 to February 28. ns, non-significant; PID, primary immunodeficiency; PPS-2, per protocol set with complete responses to seasonal questions; SD, standard deviation; WPAI, Work Productivity and Activity Impairment questionnaire

in Japan may have reduced transmission of several infectious diseases, including rubella and influenza [14]. There is also some evidence that the circulation of other respiratory viruses, including those often considered "seasonal", may have been impacted by the COVID-19 pandemic [23, 24]. In addition, although it is impossible to quantify the exact effect posed by climate, one of the most ubiquitous sources of external variation influencing this study might be global warming, which appears to be driving longer and hotter summers, shorter and warmer winters, and shorter springs and autumns in the northern hemisphere [25].

The majority of participants in this study were recruited in 2022 and were tracked for one year, during which measures for prevention of COVID-19 infection were starting to be relaxed as vaccinations increased in Japan. Although mask wearing was never mandated in Japan, it was recommended for most of the study period (up until March 2023), and the proportion of the population who wore masks was high compared with other countries during the pre-vaccination period [26]. The Japanese national COVID-19 vaccination program began in 2021, and by August 2022 around 80% of the population had received two doses of vaccine [27]. Unfortunately, the data collected in our study did

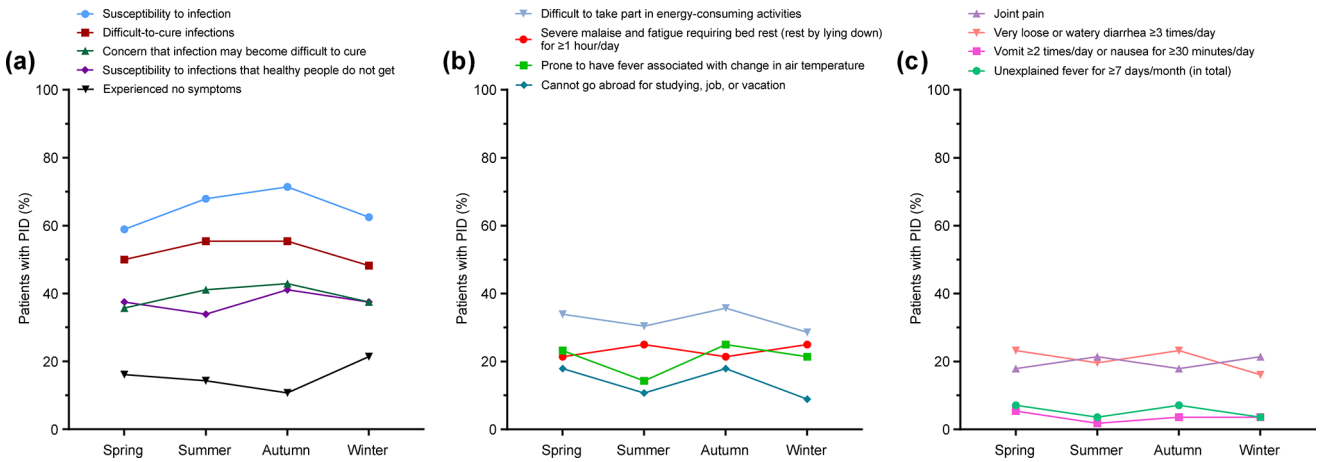

Fig. 4 Limitations of daily living in patients with PID related to symptoms (PPS-2, $N=56$). (**a**) Symptoms associated with infections (also includes patients who experienced no limitations related to symptoms); (**b**) Symptoms associated with energy limitations; (**c**) Other symptoms. Spring was defined as March 1 to May 31, summer as June 1 to August 31, autumn as September 1 to November 30, and winter as December 1 to February 28. PID, primary immunodeficiency; PPS-2, per protocol set with complete responses to seasonal questions

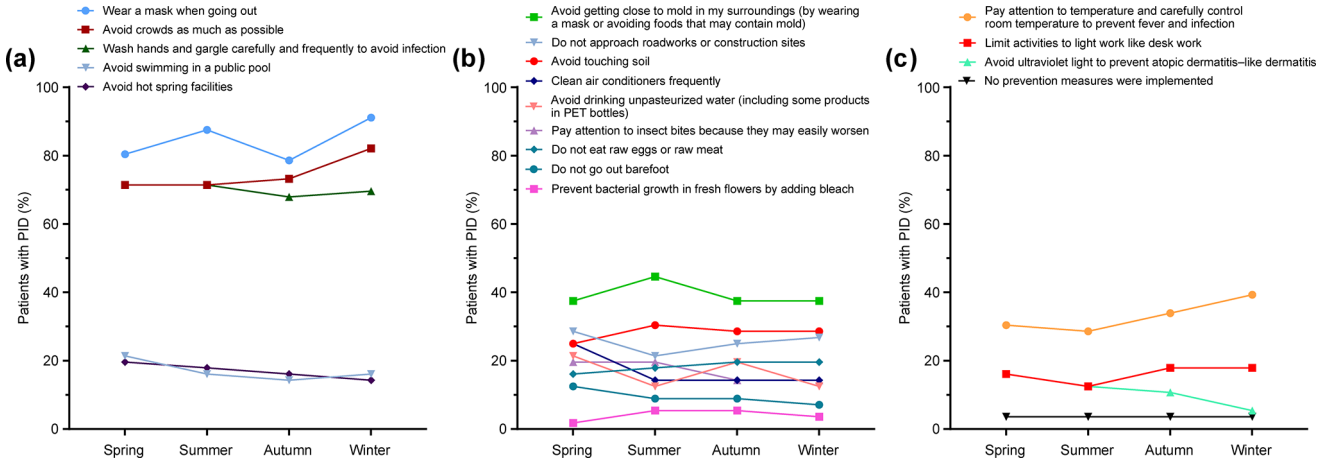

Fig. 5 Limitations of daily living in patients with PID related to prevention of symptoms (PPS-2, $N=56$). (**a**) Reducing risk of infection from other people; (**b**) Prevention of infection from environmental sources; (**c**) Efforts to maintain physical condition and a stable environment (also includes patients who did not take any preventive measures). Spring was defined as March 1 to May 31, summer as June 1 to August 31, autumn as September 1 to November 30, and winter as December 1 to February 28. PET, polyethylene terephthalate; PID, primary immunodeficiency; PPS-2, per protocol set with complete responses to seasonal questions

not include vaccination status of the participants, and it is unclear how vaccination, mask wearing, or reduced social contact may have factored into patients' perception of their disease symptoms, behavior, HR-QOL, or work productivity. A previous study of patients with common variable immunodeficiency, one of the most common PID disorders, found that there was a deterioration in all dimensions of a disease-specific HR-QOL measurement scale during the COVID-19 pandemic [28].

This prospective observational study of patients with PID and healthy volunteers was conducted over a full year, in order to assess seasonal variation in HR-QOL and workplace impairment. In addition, the study used several validated, reliable scales to assess HR-QOL and workplace impairment. Limitations of this study include that the generalizability of the results may be limited owing to (i) the small sample size in this study, and (ii) the focus on Japanese patients, who may differ from patients in other countries. The small sample size may have contributed to skewed or biased results. Furthermore, because of the regional differences in climate, seasonal effects may have been difficult to detect with patients who were recruited from throughout Japan. In addition, all data included in this analysis are patient-reported, and reports of symptoms have not been medically verified. Although patients with different disease classifications are included within the patients with PID group, the descriptive data, SF-36, EQ-5D-5L, and WPAI results were analyzed and reported for the patients with PID

group as a whole. As disease status, treatment method, disease progression, and prognosis may differ within the different disease classifications, our data may not reflect the reality for every disease classification within the patients with PID group. There is also a possibility that because the participants were given the same questionnaires multiple times, there may have been a memory effect bias. As previously discussed, this study was conducted during the COVID-19 pandemic, which may have had an impact on responses from both patients with PID and healthy volunteers.

In conclusion, in this one-year prospective observational study, patients with PID had a lower quality of life all year round and were more socially, physically, and mentally stressed in all seasons compared with healthy people. Patients with PID were affected by their condition and used a variety of methods to prevent infectious diseases in all seasons, making it difficult to observe any seasonal variations.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s10875-025-01869-z.

Acknowledgements The authors would like to thank all study participants. The authors acknowledge the medical writing assistance provided by Koa Webster, PhD, CMPP, and Rebecca Lew, PhD, CMPP, of ProScribe – Envision Pharma Group (funded by Takeda Pharmaceutical Company Limited). ProScribe's services complied with international guidelines for Good Publication Practice. The authors also acknowledge the contributions of Yoji Sasahara of Tohoku University and members of the non-profit organization PID Tsubasa-No-Kai, for participant enrollment, Naoyuki Takano of 3H Medi Solutions Inc. for project management, Akane Murakami of 3H Medi Solutions Inc. for sub-project management, Hajime Yamakage of 3H Medi Solutions Inc. for statistical analysis and medical writing of the study report, and Nana Ogawa of 3H Clinical Trial Inc. for data management.

Author Contributions All authors participated in the interpretation of study data, and in the drafting, critical review, and approval of the final version of the manuscript. N.O. developed the study concept. N.O. and K.N. summarized the medical needs for the study. T.K., H.K., M.I., M.G., and S.N. were involved in the protocol development. All authors participated in creation of the statistical analysis plan and/or the clinical study report. T.K., H.K., M.I., and S.O. were investigators in the study and were involved in subject enrollment.

Funding This study was funded by Takeda Pharmaceutical Company Limited. Takeda Pharmaceutical Company Limited was involved in the study design, data collection, data analysis, preparation of the manuscript, and the decision to submit for publication. Takeda Pharmaceutical Company Limited also funded the medical writing assistance provided by ProScribe – Envision Pharma Group.

Data Availability The datasets, including the redacted study protocol, redacted statistical analysis plan, and individual participants data supporting the results reported in this article, will be made available within three months from initial request, to researchers who provide a methodologically sound proposal. The data will be provided after its de-identification, in compliance with applicable privacy laws, data protection and requirements for consent and anonymization.

Declarations

Ethical Approval The study was performed in line with the principles of the Declaration of Helsinki. Approval of the protocol, informed consent form, and study questionnaires was granted by the Ethics Committee of the Japan Conference of Clinical Research, and the study was registered at the University hospital Medical Information Network clinical trials registry (ID: UMIN000045622).

Consent to Participate Written informed consent was provided online by all participants or their legal representative.

Consent for Publication Not applicable.

Competing Interests T.K. and H.K. have received honoraria from Takeda Pharmaceutical Company Limited. N.O., K.N., and M.G. are employees and minor shareholders of Takeda Pharmaceutical Company Limited. S.N. has received consulting fees from Takeda Pharmaceutical Company Limited. M.I. and S.O. have no competing interests to declare.

References

1. Poli MC, Aksentijevich I, Bousfiha AA, Cunningham-Rundles C, Hableton S, Klein C, et al. Human inborn erros of immunity: 2024 update on the classification from the International Union of Immunologic Societies Expert Committee. J Hum Immun. 2025;1(1):e20250003. https://doi.org/10.70962/jhi.20250003
2. Tangye SG, Al-Herz W, Bousfiha A, Cunningham-Rundles C, Franco JL, Holland SM, et al. Human inborn errors of immunity: 2022 update on the classification from the International Union of Immunological Societies Expert Committee. J Clin Immunol. 2022;42(7):1473–507. https://doi.org/10.1007/s10875-022-01289-3.
3. Seidel MG, Kindle G, Gathmann B, Quinti I, Buckland M, van Montfrans J, et al. The European Society for Immunodeficiencies (ESID) Registry working definitions for the clinical diagnosis of inborn errors of immunity. J Allergy Clin Immunol Pract. 2019;7(6):1763–70. https://doi.org/10.1016/j.jaip.2019.02.004.
4. Cunningham-Rundles C. Key aspects for successful immunoglobulin therapy of primary immunodeficiencies. Clin Exp Immunol. 2011;164(2):16–9. https://doi.org/10.1111/j.1365-2249.2011.04390.x
5. McCusker C, Upton J, Warrington R. Primary immunodeficiency. Allergy Asthma Clin Immunol. 2018;14(Suppl 2):61. https://doi.org/10.1186/s13223-018-0290-5.

6. Espanol T, Prevot J, Drabwell J, Sondhi S, Olding L. Improving current immunoglobulin therapy for patients with primary immunodeficiency: quality of life and views on treatment. Patient Prefer Adherence. 2014;8:621–9. https://doi.org/10.2147/ppa.S60771.
7. Berg AK, Diseth TH, Abrahamsen TG, Halvorsen K, Reinfjell T, Erichsen HC. Primary antibody deficiency: the impact on the quality of life and mental health of affected children and their parents. Acta Paediatr. 2021;110(5):1645–52. https://doi.org/10.1111/apa.15752.
8. Jiang F, Torgerson TR, Ayars AG. Health-related quality of life in patients with primary immunodeficiency disease. Allergy Asthma Clin Immunol. 2015;11:27. https://doi.org/10.1186/s13223-015-0092-y.
9. Peshko D, Kulbachinskaya E, Korsunskiy I, Kondrikova E, Pulvirenti F, Quinti I, et al. Health-related quality of life in children and adults with primary immunodeficiencies: a systematic review and meta-analysis. J Allergy Clin Immunol Pract. 2019;7(6):1929–57.e5. https://doi.org/10.1016/j.jaip.2019.02.013
10. Ishimura M, Takada H, Doi T, Imai K, Sasahara Y, Kanegane H, et al. Nationwide survey of patients with primary immunodeficiency diseases in Japan. J Clin Immunol. 2011;31(6):968–76. https://doi.org/10.1007/s10875-011-9594-7.
11. Hosaka S, Kido T, Imagawa K, Fukushima H, Morio T, Nonoyama S, et al. Vaccination for patients with inborn errors of immunity: a nationwide survey in Japan. J Clin Immunol. 2022;42(1):183–94. https://doi.org/10.1007/s10875-021-01160-x.
12. EFPIA Japan. Primary immunodeficiency syndrome (PID). Survey on the treatment and quality of life of patients. Results of the questionnaire survey. 2018. http://efpia.jp/link/PID_E_190130.pdf. Accessed 23 Jan 2023.
13. Grassly NC, Fraser C. Seasonal infectious disease epidemiology. Proc Biol Sci. 2006;273(1600):2541–50. https://doi.org/10.1098/rspb.2006.3604.
14. Hibiya K, Iwata H, Kinjo T, Shinzato A, Tateyama M, Ueda S, et al. Incidence of common infectious diseases in Japan during the COVID-19 pandemic. PLoS ONE. 2022;17(1):e0261332. https://doi.org/10.1371/journal.pone.0261332.
15. Moriyama M, Hugentobler WJ, Iwasaki A. Seasonality of respiratory viral infections. Annu Rev Virol. 2020;7(1):83–101. https://doi.org/10.1146/annurev-virology-012420-022445.
16. Japan Meterological Agency. General Information on Climate of Japan. 2024. https://www.data.jma.go.jp/gmd/cpd/longfcst/en/tourist.html. Accessed Mar 2024.
17. Kanegane H, Ishimura M, Kawai T, Okada S, Okamatsu N, Go M, et al. Patient-reported outcomes in patients with primary immunodeficiency diseases in Japan: baseline results from a prospective observational study. Front Immunol. 2023;14:1244250. https://doi.org/10.3389/fimmu.2023.1244250.
18. Shiroiwa T, Fukuda T, Ikeda S, Igarashi A, Noto S, Saito S, et al. Japanese population norms for preference-based measures: EQ-5D-3L, EQ-5D-5L, and SF-6D. Qual Life Res. 2016;25(3):707–19. https://doi.org/10.1007/s11136-015-1108-2.
19. Fukuhara S, Bito S, Green J, Hsiao A, Kurokawa K. Translation, adaptation, and validation of the SF-36 Health Survey for use in Japan. J Clin Epidemiol. 1998;51(11):1037–44. https://doi.org/10.1016/s0895-4356(98)00095-x.
20. Reilly MC, Zbrozek AS, Dukes EM. The validity and reproducibility of a work productivity and activity impairment instrument. PharmacoEconomics. 1993;4(5):353–65. https://doi.org/10.2165/00019053-199304050-00006.
21. Herdman M, Gudex C, Lloyd A, Janssen MF, Kind P, Parkin D, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Qual Life Res. 2011;20(10):1727–36. https://doi.org/10.1007/s11136-011-9903-x.
22. Ware JE Jr, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. conceptual framework and item selection. Med Care. 1992;30(6):473–83.
23. Zeng Z, Guan W, Liu Y, Lin Z, Liang W, Liang J, et al. Different circulation pattern of multiple respiratory viruses in Southern China during the COVID-19 pandemic. Front Microbiol. 2022;12:801946. https://doi.org/10.3389/fmicb.2021.801946.
24. De Francesco MA, Pollara C, Gargiulo F, Giacomelli M, Caruso A. Circulation of respiratory viruses in hospitalized adults before and during the COVID-19 pandemic in Brescia, Italy: a retrospective study. Int J Environ Res Public Health. 2021;18(18):9525. https://doi.org/10.3390/ijerph18189525.
25. Wang J, Guan Y, Wu L, Guan X, Cai W, Huang J, et al. Changing lengths of the four seasons by global warming. Geophys Res Lett. 2021;48(6):e2020GL091753. https://doi.org/10.1029/2020GL091753
26. Nagata M, Okada Y, Nishiura H. Epidemiological impact of revoking mask-wearing recommendation on COVID-19 transmission in Tokyo, Japan. Infect Dis Model. 2024;9(4):1289–300. https://doi.org/10.1016/j.idm.2024.08.002.
27. Karako K, Song P, Chen Y, Karako T. COVID-19 in Japan during 2020–2022: characteristics, responses, and implications for the health care system. J Glob Health. 2022;12:03073. https://doi.org/10.7189/jogh.12.03073.
28. Pulvirenti F, Villa A, D'Ambrosi M, Cusa G, Quijada-Morales P, de la Fuente-Munoz E, et al. Changes in health-related quality of life in common variable immunodeficiency: an eight-year journey, including the COVID-19 pandemic. Expert Rev Clin Immunol. 2024;20(10):1269–80. https://doi.org/10.1080/1744666x.2024.2368195.