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Impact of COVID-19 on care-seeking patterns for hay fever in Japan: A retrospective claims database cohort study

To the Editor,

Hay fever is an immune-mediated systemic disorder that requires personalized treatment approaches for each symptom and factor.[1] Interestingly, the widespread adoption of mask-wearing and restrictions on outdoor activities to prevent coronavirus disease 2019 (COVID-19) transmission have inadvertently served as preventive measures for hay fever, potentially influencing symptomatology and treatment trends during the pandemic.[2] Nevertheless, a comprehensive investigation using large-scale medical data is yet to be conducted into changes in care-seeking patterns for hay fever during the COVID-19 pandemic. Thus, we evaluated changes in hay fever care-seeking patterns during the COVID-19 pandemic using a claims database.

We conducted a retrospective cohort study using data recorded in the JMDC database (JMDC Inc., Tokyo, Japan) between January 2018 and May 2021; only those individuals with continuous records during the study period were included in the analysis. We classified patients with diagnosis-related codes for hay fever who were prescribed hay fever-related medications during outpatient visits as having hay fever. Patients who were prescribed medications during the hay fever season (January–May) were defined as having hay

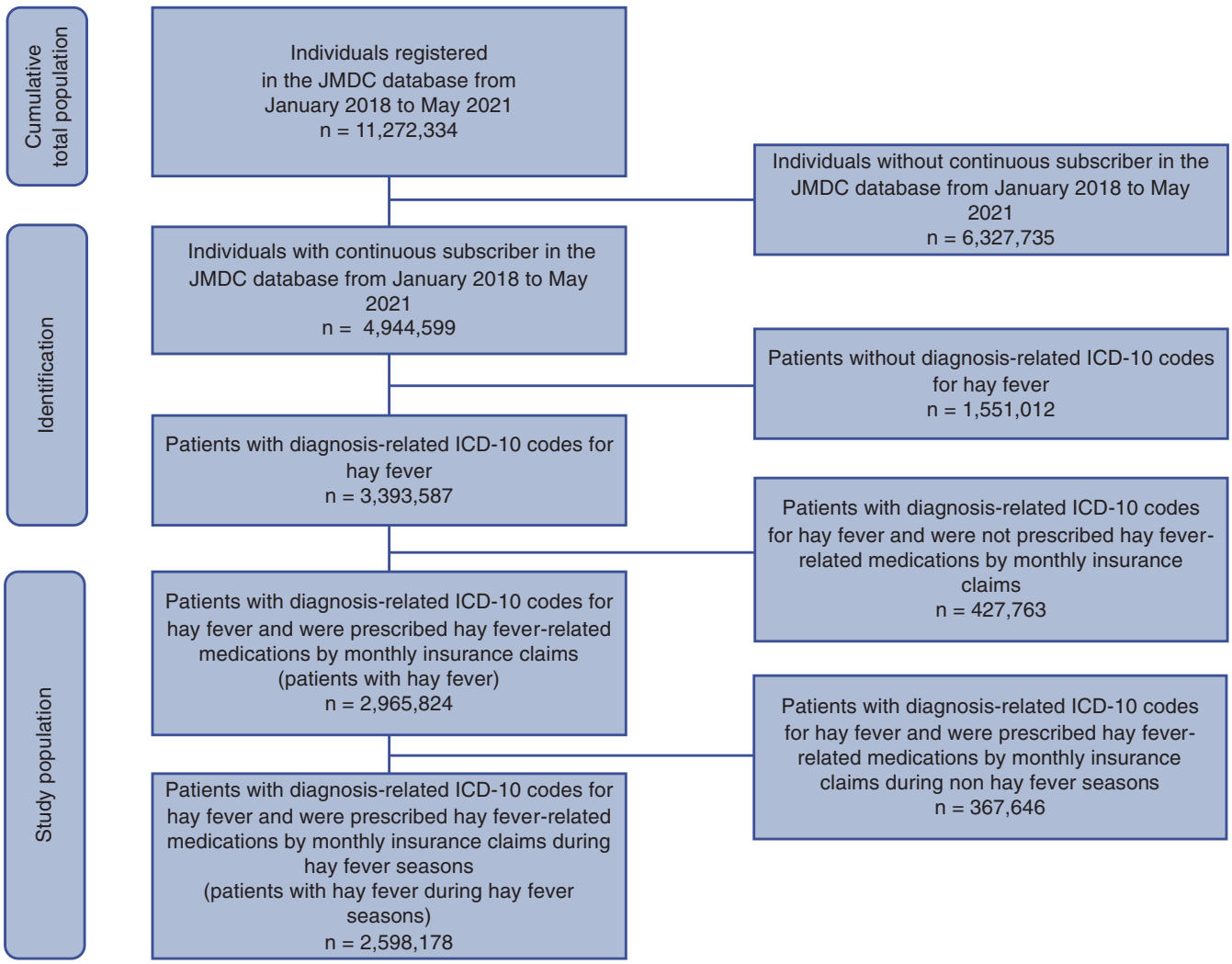

FIGURE 1 Case identification flowchart for this study. ICD-10, International Statistical Classification of Diseases and Related Health Problems 10th revision.

fever during that season. The detailed methodology is described in Appendix S1: Methods.

Figure 1 shows the case identification process for the patients included in this study. Overall, 11,272,334 individuals were registered in the JMDC database between January 2018 and May 2021. Among these, 4,944,599 were identified as continuous subscribers in the JMDC database. Subsequently, 24,722,995 were determined to be the cumulative 5-month continuous subscribers in the hay fever season. Overall, 2,598,178 individuals with hay fever during the hay fever seasons were identified. The detailed patient characteristics of the included patients are shown in Appendix S1: Results.

Figure 2A shows the monthly outpatient-visit rates for hay fever between January 2018 and May 2021.The average outpatient-visit rates during the hay fever season (January to May) in 2018, 2019, 2020, and 2021 were 12.1% (2,996,545 out of 24,722,995 individuals), 12.9% (3,196,010 out of 24,722,995 individuals), 10.3% (2,557,091 out of 24,722,995 individuals), and 10.5% (2,586,173 out of 24,722,995 individuals), respectively. These figures indicate a significant decrease in the outpatient-visit rates for hay fever during the COVID-19 pandemic (Figure 2B, $p < .001$). Figure 2C shows the number of prescriptions for hay fever-related medications between January 2018 and May 2021; the total number of these prescriptions during this period was 38,756,380. The number of prescriptions during the hay fever season (January to May) in 2018, 2019, 2020, and 2021 was 6,197,772, 6,614,412, 5,045,884, and 5,262,375 respectively. These figures indicate a decreasing trend during the COVID-19 pandemic ($p = .033$; Figure 2D).

When compared to the corresponding pre-pandemic data, our data showed that hay fever-related outpatient visits and prescriptions in hay fever seasons decreased during the pandemic. These

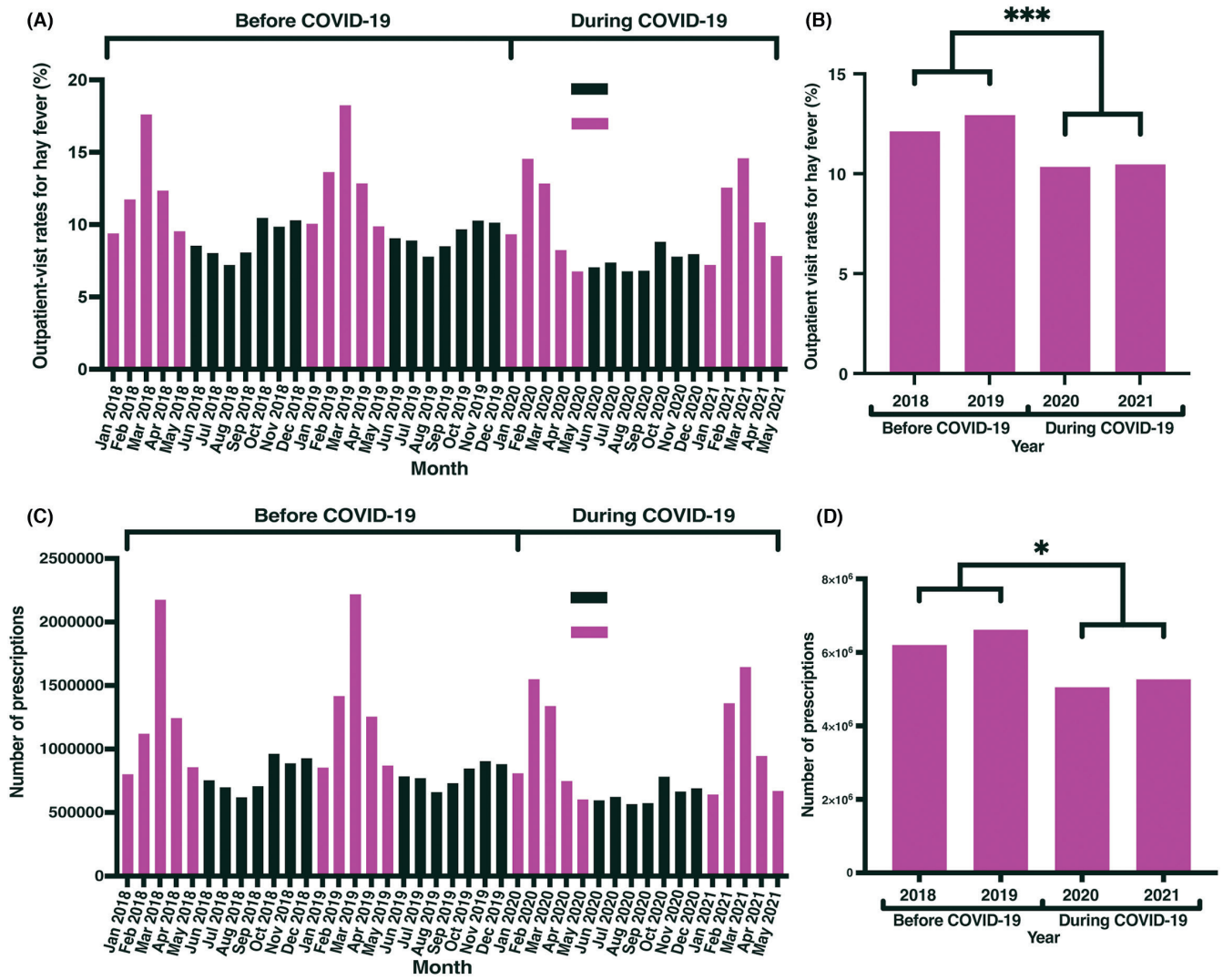

FIGURE 2 Annual changes in items during the COVID-19 pandemic. (A) Monthly visit rates for hay fever from January 2018 to May 2021 (denominator: 4,944,599 continuous subscribers in the JMDC database). (B) Average visit rates for hay fever during the hay fever season (January–May) from 2018 to 2021 (denominator: 24,722,995 cumulative 5-month continuous subscribers in hay fever season, ***$p < .001$ [χ^2 test]). (C) Monthly number of prescriptions of hay fever-related medications from January 2018 to May 2021. (D) Total number of prescriptions of hay fever-related medications during the hay fever season from 2018 to 2021 (*$p = 0.033$ [t-test]).

effects stem from efforts to minimize SARS-CoV-2 exposure,[3,4] and from government enforcement of mask usage, strict hand hygiene, and limited out-of-home activities.[5] In Japan, sales of over-the-counter (OTC) medications for allergic rhinitis in 2020 decreased from those in 2019.[6] Considering the simultaneous drop in prescriptions and OTC medication sales after the pandemic, it appears unlikely that the decrease in outpatient visits and prescriptions for hay fever was due to the available OTC remedies. Instead, the trends observed in this study were more likely the result of lifestyle changes that suppress certain hay fever symptoms.

This study has a few limitations. First, the data used in this study were limited to specific diagnoses and prescriptions. Second, providers may have prescribed medications for longer durations than those in the pre-pandemic years to minimize repeat visits to adapt to pandemic-related regulations. Third, the effect of each year's pollen dispersion on the health-seeking behavior in the patients with hay fever has not studied.

In conclusion, our findings suggest that lifestyle changes and altered perspectives brought about by the COVID-19 pandemic may have impacted hay fever symptoms and associated health care-seeking behaviors.

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AUTHOR CONTRIBUTIONS

Yasutsugu Akasaki acquired the data, analyzed and interpreted the data, and was involved in drafting the manuscript; Masao Iwagami contributed to the study design, Jaemyoung Sung was involved in drafting the manuscript; Takenori Inomata contributed to the conception and design of the study, acquisition of data, and analysis and interpretation of data. All authors contributed to revising the manuscript critically and have approved the final version for publication.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

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

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Early expansion of allergen-responsive LAP+ B regulatory cells in allergic rhinitis but not in allergic asthma subjects during allergen immunotherapy

To the Editor,

Allergen immunotherapy (AIT) is used successfully for treatment of allergic rhinitis (AR). There is also strong evidence of AIT being effective in allergic asthma (AA), when used as an add-on treatment to pharmacotherapy such as oral corticosteroids.[1] There is limited data available on immunological effects of AIT in AA compared to AR and the impact of pharmacotherapy on mechanisms of AIT. Induction of B-regulatory (Bregs) and T-regulatory (Tregs) cells are key components in tolerance induction to allergens in AIT. Bregs produce immunosuppressive cytokines IL-10 and TGF-β, which not only suppress Th2 cell responses, but also mediate induction of Tregs.[2] In this study, allergen-responsive B-cells were monitored in 7 AA and 8 AR subjects prior to and after 4, 9, and 24 months of subcutaneous allergen immunotherapy (Figure 1A). Allergen-responsiveness was determined through in vitro proliferative cell responses, indicated by loss of CFSE, to house dust mite (HDM) allergen at day 5 (Table S1). In total, 10 clusters of allergen-responsive B-cells were identified (Figure 1B). Four clusters expressed the memory marker CD27 and six did not, mostly representing naïve/transitional B-cell populations. Within those B-cell populations, a CD71+CD73$^-$CD25+LAP+ cluster was identified, consistent with a Breg phenotype. In AR subjects, the frequency of LAP+ Bregs within allergen-responsive B-cells increased at 24 months of AIT with nominal significance and was already significantly increased at 4 months (with fdr-correction, Figure 1C). This increased LAP-expression was however not observed in AA subjects. LAP is 'latency associated peptide' and serves as a marker for TGF-β expression. TGF-β is vital for induction of Tregs[2] and has important roles in Breg-induced control of autoimmunity and allergy.[3,4] Intracellular IL-10 showed a minimal overlap with LAP-expression (Figure S1), suggesting that LAP+ Breg cells produce only minimal amounts of IL-10. The increased percentage of LAP+ Bregs in AR subjects at 4 months was accompanied with a (nominal) significant decrease in CD25+CD71$^-$CD27+ memory B-cell clusters (Cluster 1 and 5; Figure 1D). Again, this change was not observed in AA subjects. The frequency of LAP+ B-cells was markedly lower in non-HDM responsive B-cells (CFSE^{hi} cells) compared to HDM-responsive B-cells (CFSE^{low} cells) and was not increased in AR or AA at 24 months of AIT (Figure S1). Enhanced HDM- or Der p 1-responsive LAP+ B-cells were also observed in two independent cohorts of 14 untreated AR patients[5] or 7 AA patients,[6] respectively, and 23 age/sex-matched healthy controls. No differences were observed between patients and their matched controls. This suggests that AIT forms a dominant trigger for the development of LAP+ B-cells, and that this may be transient.

Changes also occurred within the transcriptome of allergen-specific memory B-cells (Figure 2A). In AR subjects, there was a change in gene expression at 4 months of AIT, which did not occur in AA patients (Figure 2B). The gene ontology pathways included small GTPases-mediated signal transduction, important in cellular processes (signal transduction, cell adhesion, chemotaxis and motility, cell growth, and division), along with plasma cell, immunoglobulin (Ig) and MHC-TLR7-TLR8 pathways, necessary for germinal center forming and Ig production (Figure 2C). This was further reflected in reduced Ig heavy chain transcripts in AR subjects at 4 and 24 months of AIT, but not in AA patients (Figure 2D). Of interest, TLR7/8 pathways have been implicated in Breg function.[7]