Original Article

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The impact of COVID-19 pandemic on the utilization of ambulatory care for patients with chronic neurological diseases in Japan: Evaluation of an administrative claims database

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SUMMARY The COVID-19 pandemic has affected not only the emergency medical system, but also patients' regular ambulatory care, as such decrease in the number of patients visiting outpatient clinics decreased in 2020 than in 2019, or the ban lifting of subsequent visits by telephone for outpatient clinics since March 2020 in lieu of ambulatory care for chronic diseases. In this context, we investigate the impact of the COVID-19 pandemic on ambulatory care at Japanese outpatient clinics for patients with chronic neurological diseases during 2020. We collected data from the administrative claims database (DeSC database) covering more than 1 million individuals. Serial changes in the frequency of subsequent outpatient visits to clinics or hospitals (excluding large hospitals) for chronic ambulatory care of epilepsy, migraine, Parkinson's disease (PD), and Alzheimer's disease (AD) in 2020 were measured. As a result, since April 2020, the monthly outpatient visits for epilepsy, PD, and AD decreased slightly but significantly (approximately 0.90 in relative risk [RR]) but visits for migraine increased (RR = 1.15). Telephone visit was most frequently used in April-May, in less than 5% of monthly outpatient clinic visits for the examined neurological diseases. Outpatient visits for migraine treatment were more likely to be done by telephone than in case of other diseases (adjusted Odds ratio = 2.08). These results suggest that the impact of COVID-19 pandemic on regular ambulatory care for several chronic neurological diseases yielded different effect depending on the disease, in terms of the frequency or type of outpatient visits.

Keywords COVID-19, ambulatory care, chronic neurological disease, administrative claims data, telemedicine

1. Introduction

The global coronavirus disease (COVID-19) pandemic, since early 2020, has severely affected not only the emergency medical system in Japan (*1*), but also patient care at the outpatient clinics. To reduce the risk of COVID-19 infection, people were requested to refrain from unnecessary and nonurgent outings or from visiting crowded places, with a call to "avoid the three Cs" (closed spaces, crowded places, and close-contact settings) (*2*) based on the Act on Special Measures for Pandemic Influenza and New Infectious Diseases Preparedness and Response (*https://elaws.e-gov.go.jp/document?lawid=424AC0000000031*). People also refrained from visiting outpatient clinics (*3*), leading to a significant decrease in the number of ambulatory visits to internal medicine outpatient clinics in Japan by more than 10% in April-May 2020 compared to April-May 2019 (*4*). In addition, the ban on subsequent visits by telephone (or telephone re-examination) at outpatient clinics as an alternative to ambulatory care for chronic diseases was removed by the Ministry of Health, Labor and Welfare (MHLW) since March 2020 as an exceptional measure against the COVID-19 pandemic (*5*): in terms of reimbursement, it became newly available to claim a "subsequent visit fee" along with the "prescription fee", even in case of telephone visits.

What is concerned in these measures against COVID-19 pandemic is that they are not always feasible for some patients with chronic neurological diseases (*e.g.*, dementia, epilepsy, or Parkinson's disease), who are one of those considered as vulnerable to COVID-19 infection due to their old age or comorbid status (*6*). Since patients with chronic neurological diseases need

continuous medication and regular ambulatory care at the outpatient clinic, it is unfavorable to interrupt ambulatory care completely, even during a state of emergency (*7*). In accordance with the perceived risk of visiting outpatient clinics (*8*), some patients with neurological disease may have cancelled their routine visits, and others might have adapted by increasing the number of prescription days or by receiving ambulatory care using telephone (*9,10*), thereby attempting to decrease the frequency of direct visits to the outpatient clinic (*11*). However, because in-person visit is deemed essential especially for the ambulatory care of patients with neurological diseases (*12*), there may remain some medium- or long-term safety concerns about these measures against COVID-19.

Before attempting to evaluate the safety and efficacy of these measures to prevent COVID-19 infection for vulnerable individuals, we need to have basic data about the impact of the COVID-19 pandemic on the care for patients with chronic neurological diseases (*13*), of which evidence is limited in Japan. In a recent study using claims data from the United States, it is reported that in-person outpatient visits decreased to a degree that could not be complemented by the increased use of telemedicine (*14*). From Japan, the decrease in the number of ambulatory visits to outpatient clinics and hospitals, or the utilization rate of telephone visits, have only been reported in general remarks (*4*) or with a very limited samples (*15*), and have not been reported in detail by the area of neurology. Therefore, we herein aimed to assess the basic features of the change in care for patients with chronic neurological disease at the outpatient clinic during 2020. We used the DeSC claims database that is based on the Japanese public health insurance and comprises data on more than one million individuals in Japan. The database has a great advantage in terms of its high accessibility and analyzability compared to much larger Japanese claims databases (*e.g.*, NDB) (*16*), and thus, the use of the DeSC database in the current study would provide a starting point and an important foundation for further research.

2. Materials and Methods

2.1. Study design

This was a retrospective observational study using administrative claims data and was approved by the University of Tokyo Graduate School of Medicine Institutional Ethics Committee (ID: 11628-(3)). Informed consent is not required because this study only uses already-prepared anonymized information as required by the Act on the Protection of Personal Information in Japan (*https://elaws.e-gov.go.jp/document?lawid=415AC0000000057*). We applied for access to the DeSC database (*https://desc-hc.co.jp/archives/2188*) in March 2021, which was approved by DeSC Healthcare, Inc. (*https://desc-hc.co.jp/en*), permitting us to obtain the data in April and June 2021.

2.2. About the DeSC database

The DeSC database was built by anonymizing and processing data from the health insurance claims database provided by several Japanese public health insurers covering more than one million individuals. Three types of insurers are included: Society-managed, employment-based health insurance association (SHI), National Health Insurance (NHI), and Latter-Stage Elderly Heathcare System (we abbreviated as 'LSEHS' here) (*17*). In Japanese public health insurance system, there is no difference depending on the type of insurers regarding which clinics/hospitals to visit or regarding the range of medical treatments/practices covered by each insurer, and which type of insurer types for each individual is determined by their employment status (*17*): the SHI is provided for individuals working at large companies and their family members. NHI covers broader range of people younger than 75 years and not covered by other public health system, such as self-employed persons, freelancers, farmers, retirees, or college students. People who are 75 years or older are in principle covered by LSEHS specifically arranged for covering elderly individuals. So that the DeSC database contains patients with broad range of age and social background.

The details of individual health insurers who provided their data to the DeSC database, including their names or addresses, are completely confidential. The degree of overlap in the geographical medical areas of NHI, SHI, and LSEHS insurers is also undisclosed. The eligibility criteria for the DeSC database is as follows: insured individuals and their dependents who are in the age group of 19-74 years (in SHI), 0-74 years (in NHI), or 65 years or older (in LSEHS) as on November 30, 2021. The database includes all eligible patients' receipts claimed during the period between April 2015 and November 2021 (for SHI and NHI) or during the period between June 2018 and November 2021 for LSEHS.

As for database specifications, disease name, drugs, or medical procedures related to the following specific diseases are masked for anonymity: "designated infectious disease" such as COVID-19 or "type 1-3 infectious diseases" (*e.g.*, Ebola hemorrhagic fever, tuberculosis, SARS, or cholera) as specified in the Act on the Prevention of Infectious Diseases and Medical Care for Patients with Infectious Diseases in Japan (*https://elaws.e-gov.go.jp/document?lawid=410AC0000000114*), or "designated intractable diseases" (*18*) with a small prevalence rate.

2.3. Data preprocessing

The process of data handling and analyses were conducted using R software (version 3.5.1) in MacOS

Catalina. The preprocessing workflow is shown in Figure 1. First, the total number of insured individuals and their dependents registered by the insurers during the study period was 665,398 in SHI, 859,983 in NHI, and 300,070 in LSEHS after excluding those who had withdrawn from the insurers' list during the study period.

Among them, claims data of those who had ever visited outpatient clinic during the study period were extracted (Figure 1A). Receipts were claimed for each patient in each month of visit by each clinic or hospital, and for each type of medical setting (*e.g.*, ambulatory care, in-hospital care, or pharmacy); for our analysis, we only included the receipts claimed for ambulatory care at the facilities with less than 200 beds (Figure 1B). We limited the size of clinics or hospitals of each receipt because subsequent visit at facilities with 200 or more beds are claimed under "outpatient clinic fee" (medical practice code: 112011310) regardless of the use of telephone or any online devices, and consequently, the use of telephones for subsequent ambulatory care cannot be identified from the coding. In case of facilities with less than 200 beds, ambulatory care *via* the telephone or any electronic device can be identified, since it would be claimed as a "subsequent visit fee by telephone" (medical practice code [version in April 2020]: 112007950, 112008850, and 112023350) instead of simply "subsequent visit fee" (medical practice code: 112007410, 112015810, and 112008350). We have not considered the claims under "first visit fee" (medical practice code: 111000110) or "online medicine fee" (medical practice code: 112023210), because in case of the former, one cannot distinguish whether the examination was done by in person or *via* telephonic examination, and in the case of the latter claims, facilities are required to notify authorities in advance to start "online medicine", which have actually been hardly used by patients in this database even during the COVID-19 pandemic.

Subsequently, among the receipts claimed for ambulatory care at the outpatient clinic (Figure 1C), we considered only those that included the prescription of oral or external medications as well as the claims of "subsequent visit fee" or "subsequent visit fee by telephone" for the analysis (Figure 1D). Next, since different outpatient visits within the same month cannot be distinguished solely by each receipt, we additionally referred to the date of visits to differentiate between each visit. We use the term "date-based visit" to refer to the distinguished minimum unit of visits in order to conduct visit-based analyses.

2.4. Outcome definition

For the above-mentioned date-based visits, we determined the diseases for which each patient visited the

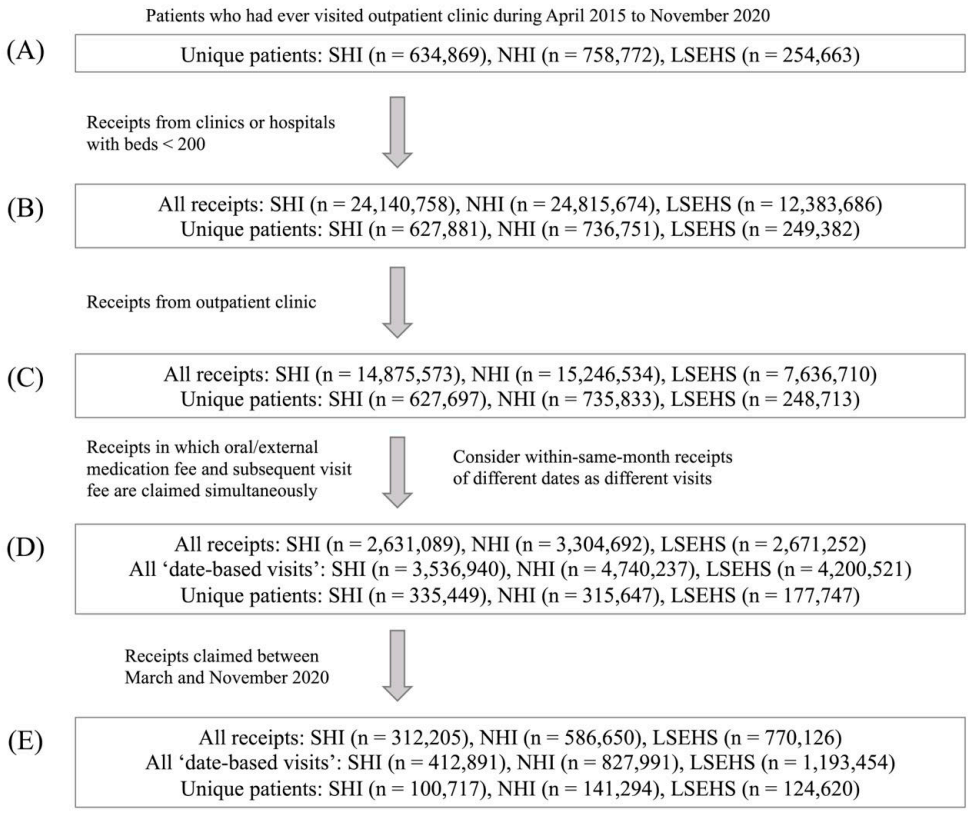

Figure 1. Data preprocessing workflow. Among approximately 1.5 million individuals who are insured by the SHI, NHI, and LSEHS insurers in the period between April 2015 and November 2020, those who had subsequent visit to outpatient clinic for their chronic neurological diseases were reviewed. Abbreviations: LSEHS, Latter-stage elderly healthcare system; NHI, National Health Insurance; SHI, society-managed, employment-based health insurance association.

outpatient clinic. Here, we specifically focus on several common neurological diseases, *i.e.*, Alzheimer's disease (AD) dementia, epilepsy, Parkinson's disease (PD), and migraine. This choice of disease is mainly due to the relatively limited sample size of the database (*i.e.*, 1-1.5 million individuals) and the low prevalence rate of many neurological diseases: extremely rare diseases by which recipients of 'intractable disease medical care ticket' (18) are less than 500 had been anonymized during the database creation process. Even in case of "uncommon" neurological diseases such as spinocerebellar ataxia, myasthenia gravis, or multiple sclerosis, they cannot always be sufficiently identified in the database: for example, disease prevalence rate of 10 per 100,000 persons in a database covering 1 million individuals means the number of included patients with the disease can become much fewer than 100 throughout the study period, because of the potential risk of under-estimation of patients based on the above-defined disease definition. In addition, although very common, we did not include chronic ischemic stroke or chronic hemorrhagic stroke because they cannot always be specifically identified by the name of the medication.

We determined whether each date-based outpatient visit was related to the care of each disease, defined by fulfilling both of the following criteria: (A) medications specific to the disease of interest are prescribed (Supplementary Table S1, A, *http://www.biosciencetrends.com/action/getSupplementalData.php?ID=77*), and (B) receipt claim (monthly) includes disease names related to the disease of interest (Supplementary Table S1, B, *http://www.biosciencetrends.com/action/getSupplementalData.php?ID=77*). This is in reference to earlier studies (*e.g.*, in PD (*19,20*) or epilepsy (*21,22*)). We referred to the Anatomical Therapeutic Chemical classification system (ATC code) for identifying medications (A) and the 10th version of the International Statistical Classification of Diseases and Related Health Problems (ICD-10) for identifying diseases (B).

2.5. Statistical analyses

In Japan, COVID-19 positive case was first confirmed on January 16, 2020, and daily positivity gradually increased. Then the daily number of COVID-19 positivity started to increase exponentially since late March 2020, leading to the first-time declaration of State of Emergency (*6*). The first wave peaked out in the mid of April 2020. The next State of Emergency has not been declared until January 8, 2021 in the mid of third wave of COVID-19 positivity. Based on such serial events, in this study we investigated the serial changes in the monthly outpatient visits especially in terms of the first State of Emergency.

As described above, the DeSC database comprises three sub-datasets (*i.e.*, SHI, NHI, and LSEHS datasets), corresponding to data obtained from different types of insurers. The population covered by these insurers have different disease frequencies partly due to the differences in age distribution (as mentioned in the Results section) and social background. Therefore, we conducted the same analysis on each of the three datasets independently, and then comparatively described the results. In this study, we performed the following analyses.

i) Serial monthly changes in the date-based visit of neurological diseases of interest, in terms of before and after the nationwide declaration of a state of emergency (*6*) in 2020.
ii) Utilization rate of telephone visits among date-based subsequent visits since March 2020.
iii) Facility-dependent variance in the utilization (frequency and rate) of telephone visits.
iv) Features which promoted or discouraged the use of telephone in subsequent ambulatory care.

First, we evaluated the overlap in SHI, NHI, and LSEHS insurers among all visits in each facility, because the degree of overlap in the geographical medical areas of these insurers is uncertain. In Japan there is no restriction on patients regarding which hospitals to visit regardless of the type of health insurance ("free access"); therefore, if many facilities had received only the patients covered by one type of insurer, the locations of that type of insurer should be interpreted as geographically located away from others. Such insurer-deviation in each facility F is evaluated by the asymmetry index (AI), calculated by the following formula:

$$AI_F = \left| \frac{max\{N_{F,SHI}, N_{F,NHI}, N_{F,LSEHS}\} - min\{N_{F,SHI}, N_{F,NHI}, N_{F,LSEHS}\}}{max\{N_{F,SHI}, N_{F,NHI}, N_{F,LSEHS}\} + min\{N_{F,SHI}, N_{F,NHI}, N_{F,LSEHS}\}} \right|$$

where $N_{F,insurance}$ is the number of patients by each insurance at a certain facility F, and $0 \leq AI_F \leq 1$. If AI is not 1 in many of the facilities, the residing locations of patients insured by SHI, NHI, and LSEHS can then be interpreted as geographically overlapping with each other.

For Analysis [1], serial change at each month since the nationwide declaration of a state of emergency (first-time on April 7, 2020) in comparison with the previous year was measured by relative risk (RR), calculated by the following formula:

$$RR_m = \left(\frac{N_{m,2020}}{N_{m,2020} + N_{Jan,2020}} \right) \Big/ \left(\frac{N_{m,2019}}{N_{m,2019} + N_{Jan,2019}} \right)$$

where $N_{m,2020}$ denotes the total number of date-based visits of a certain disease of interest in month m of 2020. As a reference month, we used the total number of date-based visits in January 2019 and January 2020. The RR values from RR_{Mar} through RR_{Nov} were

synthesized by conducting generic inverse variance meta-analysis, to obtain synthesized RR (RR_{syn}) in a random effect model. When the upper 95% of the synthesized RR was less than 1, or when the lower 95% of the synthesized RR was larger than 1, the number of date-based visits was considered to have significantly changed compared to the previous year (March-November 2019). To calculate RR and its 95% CI, we used the R packages {*epitools*} (*23*) and {*meta*} (*24*).

In addition, we also applied interrupted time-series analysis (ITSA) (*25*) for Analysis [1], based on the impact model where there was a significant decline in the level along with the declaration of a state of emergency (in April 2020), while serial trend was maintained. The Poisson regression formula for the ITSA is as follows:

$$log(total\ count\ N\ of\ outpatient\ visit\ /month) = intercept + \beta_1 \cdot (month\ number\ since\ December\ 2018) + \beta_2 \cdot (being\ period: April{\sim}November\ 2020) + \beta_3 \cdot (dummy\ variable\ of\ month) + offset(total\ number\ of\ outpatient\ visits\ (or\ insured\ people)\ in\ each\ month)$$

where the term "*month number since December* 2018" denotes long-term trend (slope) of the month before impact, and the term "*being period: April~November* 2020" corresponds to the temporal change in the intercept as a consequence of the declaration of state of emergency. Seasonality in the serial change of monthly outpatient clinic visits is taken into account by the term "*dummy variable of month*". The visit count is also influenced by the total number of monthly insured individuals and is thus considered as the offset term. As in RR, when the upper 95% confidence interval (CI) of the adjusted odds ratio (OR) was less than 1, or when the lower 95% CI of the adjusted OR was larger than 1, the factor was considered to be significantly associated with the utilization of telephone visits in the regular outpatient visit (excluding the first-time one).

Whether telephone visit is used during regular ambulatory care depends not only on the patients' intention but also on the status of each facility (clinic/hospital) to enable the use of telephone visits, as well as any compelling need to use telephone visits, such as forced temporary closure of outpatient clinics due to the nosocomial outbreak of COVID-19 (*26*). This means that the utilization rate would vary depending on each facility. In Analysis [3], we calculated the coefficient of variation (CV_D) of each disease D to measure the facility-dependent variance in the utilization rate of telephone visits between March and November 2020, using the following formula:

$$T_k = total\ number\ of\ subsequent\ visits\ for\ D\ by\ telephone\ in\ facility\ k\ during\ the\ period$$

$$V_k = total\ number\ of\ subsequent\ visits\ for\ D\ in\ facility\ k\ during\ the\ period$$

$$CV_D = standard\ deviation\left(\frac{T_1}{V_1}, \frac{T_2}{V_2}, \ldots \frac{T_F}{V_F}\right) \Big/ mean\left(\frac{T_1}{V_1}, \frac{T_2}{V_2}, \ldots \frac{T_F}{V_F}\right)$$

where F ($1 \leq k \leq F$) is the total number of facilities, $T_k \geq 0$, and $V_k \geq 3$. We regarded the use of telephone visits for disease D as variable if $CV_D > 1$.

In Analysis [4], we merged SHI, NHI, and LSEHS datasets together, and applied a generalized linear mixed model to examine which features are associated with the use of telephone visits among all the date-based subsequent outpatient visits. Since there is a variance in the number of telephone visits used depending on the clinic or hospital (as observed in Analysis [3]), as well as differences between the two datasets in terms of age distribution and disease frequency, we incorporated the factor of patient care facility and the insurer of each patient into the mixed effects model as random effect terms. The model is described by the following formula (*27*):

$$Odds = \frac{P(Y_i = 1 \mid x_i, z_i)}{P(Y_i = 0 \mid x_i, z_i)} = exp(x_i^T \beta + z_i^T u)$$

where Y_i represents the binomial status of the use or non-use of telephone visits in the subsequent outpatient visits i for any diseases, β is the vector of fixed effect parameters, x_i is the covariate matrix for fixed effects, u is the vector of random effect parameters, and z_i is the covariate matrix of random effects. Covariates to measure fixed effects include patient's age at the time of outpatient clinic visit, sex of the patient, and binomial status whether the visit is for seeking care for a certain disease of interest. Covariates used to measure random effects (as the random intercept) denote the factor of the clinic or hospital where the receipt was claimed, and the type of insurance (*i.e.*, SHI, NHI, and LSEHS). For the multilevel analysis, we used the R package {*lme4*} (*28*). We have not conducted the Analysis [4] for the patient-based count table because of the difficulty in adjusting the factors influencing facility visits (*e.g.*, some patients regularly visit several different facilities in the same month).

3. Results

3.1. Basic demographic characteristics

During the period between March and November 2020, we included 412,891 date-based outpatient clinic visits claimed for 100,717 unique patients in SHI, 827,991 date-based visits claimed for 141,294 unique patients in NHI, and 1,193,454 date-based visits claimed for 124,620 unique patients in LSEHS (Figure 1E). As expected, the AI value was mostly 1 in many facilities (mean = 0.999, 95%-tile = 1.000, and 99.7%-tile = 1.000).

The summary demographic characteristics of eligible date-based visits and unique patients during the period between March and November 2020 are described in Table 1 (data during all eligible period

Table 1. Basic demographic characteristics of all eligible subsequent outpatient visits/patients from SHI, NHI, and LSEHS

(A) Summary by outpatient visits	SHI visits Mar.-Nov. 2020	NHI visits Mar.-Nov. 2020	LSEHS visits Mar-Nov 2020
N	412,891	827,991	1,193,454
Age (in Dec 2020)	54.5 (44.9-63.1)	69.2 (62.8-72.3)	82.5 (78.6-87.0)
Sex (female)	192,132 (46.5 %)	447,245 (54.0 %)	704,240 (59.0 %)
Telephone re-examination used	1,116 (0.3 %)	4,613 (0.6 %)	4,279 (0.4 %)
neurological diseases			
Alzheimer's disease	119 (0.0 %)	1,278 (0.2 %)	24,475 (2.1 %)
epilepsy	1,337 (0.3 %)	8,952 (1.1 %)	4,687 (0.4 %)
Parkinson's disease	348 (0.1 %)	5,032 (0.6 %)	3,673 (0.3 %)
migraine	837 (0.2 %)	741 (0.1 %)	206 (0.0 %)
(B) Summary by unique patients	SHI patients who have vis-ited during Mar-Nov 2020	NHI patients who have visited during Mar-Nov 2020	LSEHS patients who have visited during Mar-Nov 2020
N	100,717	141,294	124,620
Age (in Dec 2020)	51.0 (40.2-59.8)	68.8 (60.6-72.1)	82.5 (78.6- 87.1)
Sex (female)	49,076 (48.7 %)	80,002 (56.6 %)	76,616 (61.5 %)
Telephone re-examination used	861 (0.9 %)	1,783 (1.3 %)	2,295 (1.8 %)
neurological diseases			
Alzheimer's disease	27 (0.0 %)	239 (0.2 %)	3,778 (3.0 %)
epilepsy	222 (0.2 %)	1,273 (0.9 %)	724 (0.6 %)
Parkinson's disease	54 (0.1 %)	589 (0.4 %)	546 (0.4 %)
migraine	275 (0.3 %)	194 (0.1 %)	49 (0.0 %)

LSEHS, Latter-stage elderly healthcare system; NHI, National Health Insurance; SHI, society-managed, employment-based health insurance association.

is provided in Supplementary Table S2, *http://www.biosciencetrends.com/action/getSupplementalData.php?ID=77*). When categorized by visits (Table 1A), the median age of patients covered by each insurer clearly differed: median 54.5 years in SHI, 69.2 years in NHI, and 82.5 years in LSEHS. The proportion of female patients also differed: 46.5% in SHI, 54.0% in NHI, and 59.0% in LSEHS.

Before the deregulation of telephone visits on March 2020, among subsequent outpatient visits, telephone was used in 0.07% (2,194/3,124,049) in SHI, 0.02% (768/3,911,478) in NHI, and 0.04% (1,228/3,007,067) in LSEHS throughout the reviewed period; the utilization rate of telephone re-examination increased to 0.30% (1,116/412,891) in SHI, 0.58% (4,613/827,991) in NHI, and 0.36% (4,279/1,193,454) in LSEHS during the period between March and November 2020.

3.2. Serial changes in outpatient clinic visits

First, we reviewed serial changes in the date-based outpatient clinic visits within the last two years (December 2018-November 2020), as shown in Figure 2. Visual inspection revealed that the number of monthly visits for any disease in all insurers (Figure 2A, 2E), for epilepsy or PD in NHI (Figure 2C, 2G), or for AD in LSEHS (Figure 2D, 2H) appeared to be decreasing since the timing of April 2020.

This was statistically validated by RR and ITSA (without offset term), showing similar results (Table 2): regular outpatient visits for any diseases decreased both in synthesized RR (Table 2A) and in ITSA intercept term (column '*impact in April 2020*') regardless of the type of insurers (Table 2B). In addition, in terms of neurological diseases, in SHI, visits for migraine showed slight but significant increase in both RR (Table 2A) and ITSA (Table 2B), and other neurological diseases showed no significant change. In NHI and LSEHS, the number of monthly visits for all neurological diseases except for migraine significantly decreased in both RR (Table 2A) and ITSA (Table 2B).

In ITSA models including offset term (Supplementary Table S3, *http://www.biosciencetrends.com/action/getSupplementalData.php?ID=77*), there was a significant increase in the number of visits for epilepsy, PD, and migraine in proportion to all ambulatory visits (excluding the first-time ones).

3.3. Facility-dependent variability in telephone re-examination use

We calculated the *CV* of the telephone re-examination rate, revealing high facility-dependent variance (*CV* > 1) in the rate of telephone re-examination used in outpatient visits for each disease: CV_{AD} = 4.69, $CV_{epilepsy}$ = 4.63, CV_{PD} = 4.64, $CV_{migraine}$ = 3.37, while CV_{any} = 9.64 (Figure 3A).

Figure 3B and Figure 3C are bar plots showing the number of outpatient clinic visits by facility (clinics or hospitals) where telephone re-examination "subsequent visit fee" had been claimed from March to November 2020 for 10 or more visits (SHI, NHI, and LSEHS

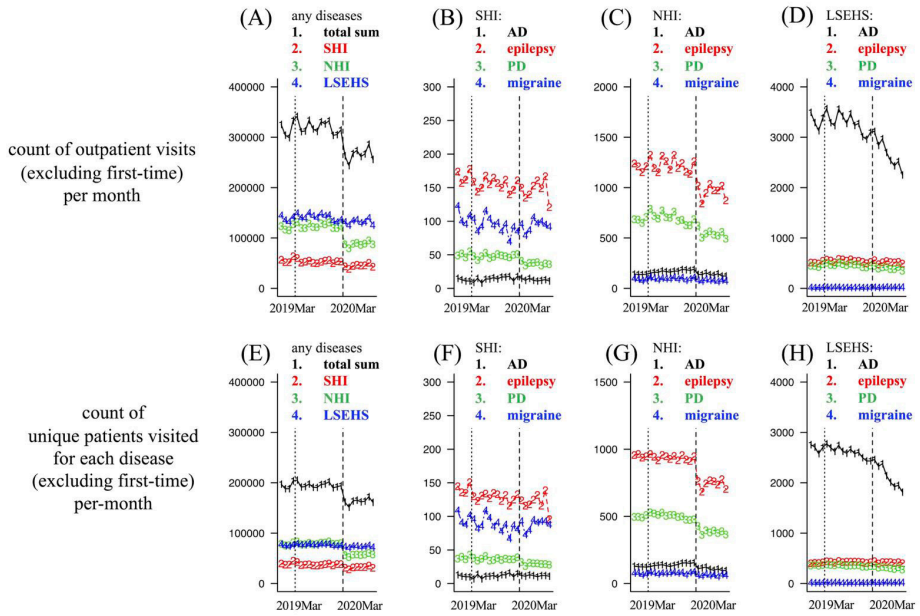

Figure 2. Serial change in the monthly count of visits / patients where subsequent visit fee were claimed, since December 2018 to November 2020. Monthly count by visits **(A) - (D)** and count by unique patients **(E) - (H)**. We calculated the count of unique patients of each month by enumerating those who have ever visited for the disease of interest and have any visits within the month. The vertical dashed line shows the timing of Declare of State of Emergency in early April 2020, and the vertical dotted line indicates the same day in 2019. Abbreviations: AD, Alzheimer's disease; LSEHS, Latter-stage elderly healthcare system; NHI, National Health Insurance; PD, Parkinson's disease; SHI, society-managed, employment-based health insurance association.

Table 2. Change in the number of monthly outpatient visits: RR and ITSA

(A) Synthesized RR results Visits for	RR in SHI	RR in NHI	RR in LSEHS
AD dementia	0.841 (0.694-1.018)	0.806 (0.753-0.863)*	0.933 (0.899- 0.968)*
Epilepsy	1.025 (0.973-1.08)	0.911 (0.875-0.947)*	0.95 (0.924-0.977)*
PD	0.945 (0.853-1.047)	0.914 (0.884-0.945)*	0.948 (0.919-0.978)*
Migraine	1.148 (1.077-1.225)*	0.987 (0.921-1.057)	1.032 (0.905-1.175)
any diseases	0.932 (0.904-0.961)*	0.834 (0.797-0.873)*	0.964 (0.953-0.976)*

*Upper 95% CI < 1 or lower 95% CI > 1.

(B) ITSA results (without offset term)	coefficients (95% CI)	
Visits for	Serial trend (slope)	Impact in April 2020
SHI		
AD dementia	1.021 (0.99-1.053)	0.737 (0.465-1.166)
Epilepsy	0.992 (0.983-1.001)	1.037 (0.905-1.187)
PD	0.997 (0.981-1.014)	0.803 (0.627-1.030)
Migraine	0.982 (0.97-0.993)*	1.205 (1.013-1.434)*
any diseases	0.996 (0.995-0.996)*	0.881 (0.875-0.888)*
NHI		
AD dementia	1.024 (1.014-1.033)*	0.626 (0.546-0.717)*
Epilepsy	1 (0.996-1.003)	0.775 (0.738-0.815)*
PD	0.997 (0.992-1.001)	0.777 (0.727-0.831)*
Migraine	1.008 (0.996-1.02)	0.722 (0.605-0.862)*
any diseases	1.002 (1.002-1.002)*	0.687 (0.684-0.690)*
LSEHS		
AD dementia	0.994 (0.992-0.996)*	0.851 (0.826-0.878)*
Epilepsy	1.001 (0.996-1.007)	0.914 (0.849-0.984)*
PD	0.998 (0.993-1.004)	0.856 (0.789-0.928)*
Migraine	1.007 (0.98-1.036)	1.059 (0.715-1.569)
any diseases	0.999 (0.999-0.999)*	0.924 (0.92-0.929)*

*Upper 95% CI < 1 or lower 95% CI > 1. CI, confidence interval; ITSA, interrupted time-series analysis; LSEHS, Latter-stage elderly healthcare system; NHI, National Health Insurance; RR, relative risk; SHI, society-managed, employment-based health insurance association.

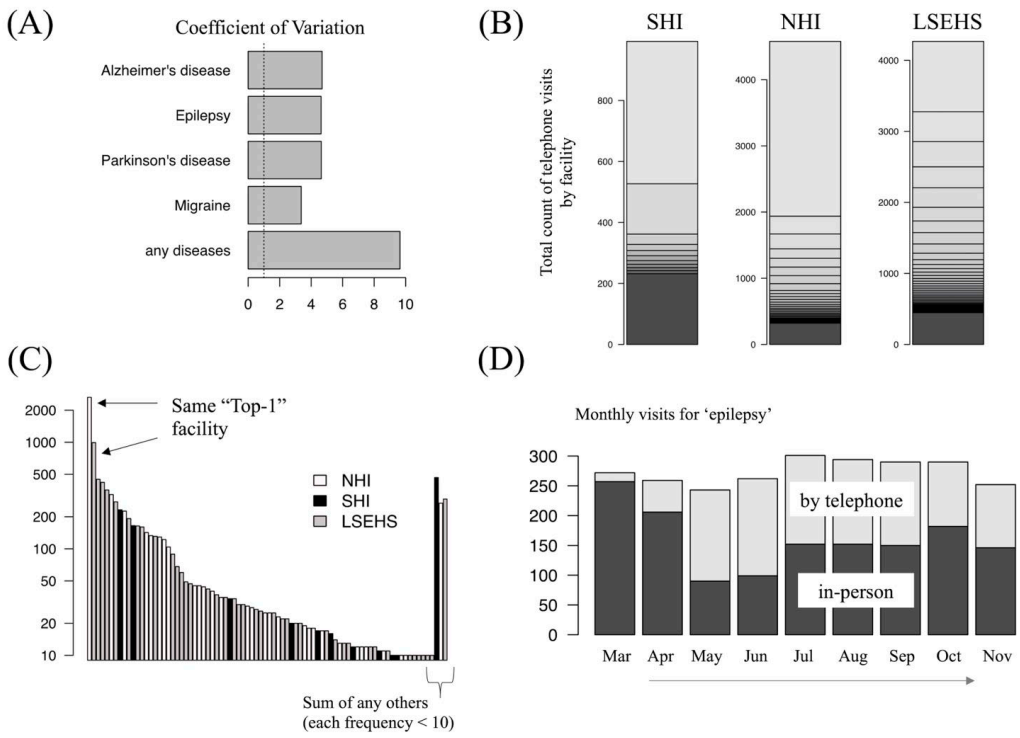

Figure 3. Facility-dependent variance in the number/rate of telephone re-examination used in subsequent outpatient visits between March and November 2020. (A) Degree of facility-dependent variation in the rate of telephone re-examination used for each disease. **(B)** Stacked bar plot of actual number of telephone re-examination used in each facility, summarized by the type of insurer and its parallel bar chart **(C)**. **(D)** Serial changes in the number of visits for ambulatory care for epilepsy at the 'Top-1' outpatient clinic. Abbreviations: SHI, society-managed, employment-based health insurance association; NHI, National Health Insurance; LSEHS, Latter-stage elderly healthcare system.

visits were separately counted in each facility). A large variability in the count was observed, and notably, the one facility which provided the largest number of telephone re-examination in NHI and LSEHS ('top-1' facility) accounted for 36.3% of all telephone re-examination visits in this database since March 2020 (Figure 3C). When we further focused on the "top-1" facility in terms of its care for epilepsy (Figure 3D), the proportion of telephone re-examination use clearly increased in May 2020.

3.4. Telephone re-examination utilization

Overall, visits for any diseases had an approximately 1% of utilization rate of telephone visits at best in May 2020, regardless of the type of insurers (Supplementary Figure S1, *http://www.biosciencetrends.com/action/getSupplementalData.php?ID=77* A). Serial changes in the utilization rate of telephone visits in subsequent ambulatory care for neurological diseases in 2020 are plotted in Figure 4. In SHI (Figure 4A, D), among the neurological diseases of interest, telephone was most frequently used in visits for AD dementia in April, followed by migraine in May (Figure 4A). On the other hand, in NHI and LSEHS, telephone re-examination was most frequently used in visits for epilepsy among the neurological diseases of interest (Figure 4B-C, E-F), followed by AD dementia.

3.5. Factors associated with the use of telephone re-examination

We shall now examine which features of each visit may have contributed (or not contributed) to the use of telephone re-examination in regular visits. The results are shown in Table 3, where each row shows the result of fixed effect coefficient and its 95% CI in each model (models 1-4, depending on the type of disease as covariate). After adjusting the type of insurers and the facility-specific factor, older or female patients were found to be slightly more likely to use telephone re-examination than younger or male patients consistently (adjusted Odds ratio [OR] in female (compared to male) = 1.31 (95% CI: 1.25-1.37), and adjusted OR = 1.01 (95% CI: 1.006-1.011) per 1-year older). Being regular visits for neurological diseases of interest except for migraine was not associated with the use of telephone re-examination (adjusted OR in migraine = 2.08 [95%CI: 1.52-2.84]).

4. Discussion

In this study, we analyzed an administrative claims database to investigate the influence of the COVID-19 pandemic on ambulatory care for chronic neurological diseases in Japan in 2020.

The key findings are as follows: [1] regular visits

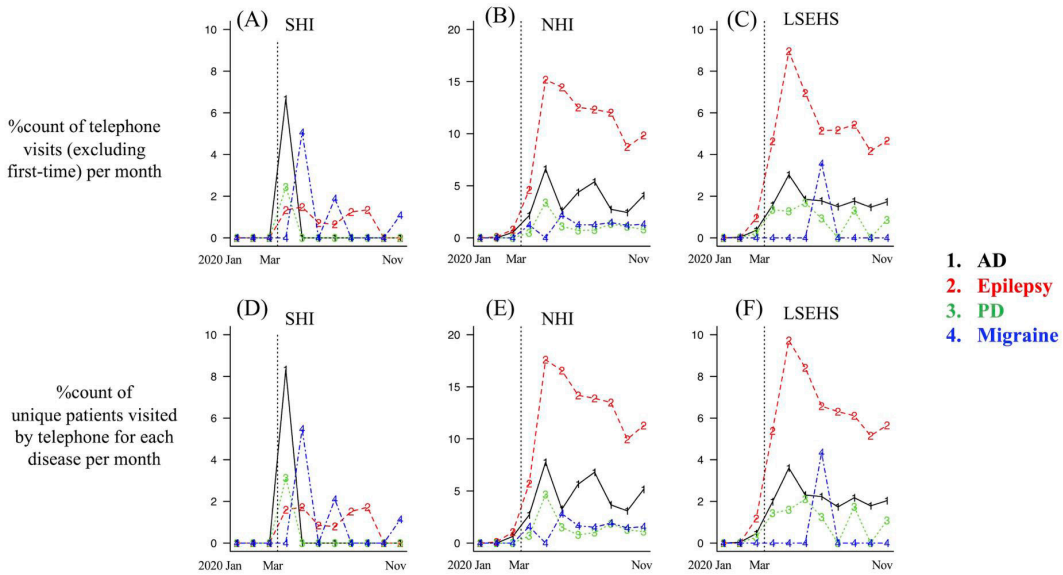

Figure 4. Serial increase in the monthly utilization rate (%) of telephone re-examination in re-examination visits for neurological diseases. Serial changes of %count by visit **(A-C)** or by unique patients **(D-F)** between January and November 2020. The vertical dotted line represents the timing of Declare of State of Emergency in April 2020. Abbreviations: AD, Alzheimer's disease; LSEHS, Latter-stage elderly healthcare system; NHI, National Health Insurance; PD, Parkinson's disease; SHI, society-managed, employment-based health insurance association.

Table 3. Results of the generalized linear mixed model for telephone visits among all (SHI + NHI + LSEHS) subsequent visits

Mixed models	Fixed-effect coefficients (in Odds ratio and 95%CI)		
	Age at each visit	Sex (female)	Being visits for the disease of interest
model 1	1.008 (1.006-1.011)*	1.308 (1.250-1.369)*	1.015 (0.901-1.144) [AD]
model 2	1.008 (1.006-1.011)*	1.309 (1.251-1.369)*	1.074 (0.984-1.173) [epilepsy]
model 3	1.008 (1.006-1.011)*	1.308 (1.251-1.367)*	0.850 (0.707-1.022) [PD]
model 4	1.008 (1.006-1.011)*	1.307 (1.249-1.367)*	2.077 (1.519-2.839)* [migraine]

*Upper 95% CI < 1 or lower 95% CI > 1. AD, Alzheimer's disease; CI, confidence interval; LSEHS, Latter-stage elderly healthcare system; NHI, National Health Insurance; PD, Parkinson's disease; SHI, society-managed, employment-based health insurance association.

for AD dementia, epilepsy, and PD mildly decreased since April 2020 in NHI and LSEHS; [2] the frequency and proportion of telephone re-examination use in ambulatory care visits for neurological diseases highly varied by each facility; [3] the telephone re-examination utilization rate generally reached its peak (approximately 5% of visits) in May 2020, after its lifting of the nationwide ban in March 2020; and [4] regular ambulatory visits for migraine were more likely to be done by telephone than visits for other diseases were. A major advantage of this study is that it used the DeSC database, which has higher accessibility and analyzability than the national database (NDB), to investigate recent claims data, despite its weakness of relatively smaller sample size. Our results thus provide basic insights about the trends in ambulatory care for chronic neurological disease patients at outpatient clinics during 2020, setting the stage for further research on the influence of COVID-19 on patients with neurological diseases.

In line with an earlier study from Japan (*4*), United States (*14*), or China (*29*) reporting reduced outpatient visits following the COVID-19 pandemic, we confirmed the decline in regular visits for AD dementia, epilepsy, Parkinson's disease, or for any diseases (Figure 2A, Table 3), presumably reflecting the social response to the COVID-19 pandemic – refraining from stepping out to reduce the risk of COVID-19 infection. For neurological disease patients who need regular visits to outpatient clinics for their requirement of continuous medications, some of them may have adapted by increasing the number of prescription days. Although the use of telephone re-examination may have led to an increase in the monthly visit count because according to the authors' observation many of the facilities available for regular visits by telephone re-examination self-regulated the prescription days to be shorter than those in case of in-person visits (*e.g.*, 30 days or so), the low utilization rate of telephone visits (Figure 4) could not have complemented the over decrease in the count of monthly visits, we suspect. It is uncertain about how many of patients with these neurological

diseases voluntarily ceased to visit hospitals and stop taking medications, and about its medium/long-term consequences.

Change in the monthly visits differed by the type of insurance. There was a decline in the monthly regular visits for AD, epilepsy, or PD in NHI or LSEHS but not in SHI (Table 3), while there was an elevation in the number of monthly visits for migraine in SHI (Table 3). This may be due to the difference in their median age distribution: older in the increasing order of SHI, NHI, and LSEHS. The perceived risk of COVID-19 infection may vary by age, as reported in a survey in the United State where more older people reported larger perception of fatality risk when infected with COVID-19 (*30*). Larger fear of death by COVID-19 infection will motivate social distancing more intensively. In addition, since mental stresses and lifestyle changes due to COVID-19 pandemic might lead to trigger migraine (*31,32*), which has in general more disease activity in younger age (*33*).

Until March 2020, the use of telephone re-examination in outpatient clinics in Japan had been largely limited, even for regular visits for chronic diseases. On February 28, 2020, the MHLW announced that they are lifting the nationwide ban on telephone re-examination for outpatient clinics as one of the exceptional measures against the COVID-19 pandemic (*5*). Aside from the initial plans to prevent COVID-19 infection risks, the consequences of lifting the ban on telephone re-examination, in terms of actual efficacy and safety, has hardly been validated in Japanese clinical settings. Although currently, there are no established guidelines, careful evaluation will be needed beforehand to determine the diseases or cases for which the use of telephone re-examination may be especially inappropriate (*12,34*). For example, patients with epilepsy and poor sleep quality were found to have an increased risk of worsening seizures during COVID-19 in Italy (*34*). Patients with neurological diseases, such as neurodegenerative diseases, often require in-person neurological examinations at outpatient clinics to be evaluated for disease progression or their current disease status, so that telephone re-examination in lieu of ambulatory care may be less appropriate for PD (*12*) compared to other neurological diseases such as epilepsy or migraine.

Overall, our study revealed that outpatient visits for ambulatory care for AD, PD, and epilepsy mildly but significantly decreased without any elevation in the utilization rate of telephone visits, while outpatient visits for ambulatory care for migraine mildly increased with higher utilization rate of telephone visits. These results showed that the impact of COVID-19 pandemic on the ambulatory care in 2020 yielded different effect depending on the disease, in terms of the frequency or type of outpatient visits. In addition, in case of AD dementia, epilepsy, and PD, potential medium/long-term risk of using telephone visits may be limited as a whole. Although the generalizability of these obtained results is limited given the relatively smaller size of claims database by nature, the degree of decline in patient visits or the utilization rate of telephone re-examination was similar to that of an earlier questionnaire survey (*4*), thereby supporting a certain level of validity in the results obtained in the current study.

Higher odds ratio of using telephone visits for migraine during COVID-19 pandemic also suggests the importance of paying attention to the treatment of migraine or other related headache patients, especially in terms of medication overuse (*35*). Although its direct evidence is limited, due to the psychological stresses following COVID-19 pandemic and the requirement of social distancing, as well as the higher convenience of telephone visits than in-person outpatient visits, might increase the frequency of migraine attack and the patients' demand for triptan drugs (*32*); such scenario is consistent with our results where outpatient visits for migraine in SHI increased after the timing of Declaration of State of Emergency (Figure 2B). In some migraine patients whose triptan demand increased, the risk of medication (or triptan) overuse elevates. In this context, we will need to evaluate the association between the incidence of medication overuse headache and the use of telephone visits (or telemedicine) under COVID-19 pandemic.

We observed very low utilization rate of telephone visits instead of conventional in-person visits for the ambulatory care of any diseases (*e.g.*, approximately 1% or less: Figure S1), and the high variability in facilities where telephone visits were used (Figure 3). As this measure was introduced as an exceptional measure against COVID-19 pandemic (*5*), the policy was insufficiently implemented throughout the overall clinics/hospitals, so that its direct effectiveness may have been insufficient by itself. Assessing facility-wise barriers/causes preventing to facilitate telemedicine may be also required as a policy consideration to promote telemedicine in the future.

Our study has several limitations. First, the disease definition of neurological diseases used in this study has not always been validated, and it is also impossible to return to the original electronic medical record for validation. The disease definitions used in this study are focused more on the content of prescriptions, which could lead to some underestimation of the actual diseases of interest: for example, patients with AD dementia do not always take anti-cholinesterase drugs because of their positive side effects or negative main effects. PD patients in their earliest stage would not be detected by our definition because they often do not receive any anti-PD medications. Furthermore, there is another concern about the overestimation of neurological diseases, especially in the case of epilepsy, since anti-epileptic drugs can sometimes be used for

other indications. For instance, valproic acid is often used for bipolar disorder or migraine prophylaxis, and carbamazepine can also be prescribed for bipolar disorder or trigeminal neuralgia.

Moreover, because the DeSC database used in this study does not disclose the details of the regions and localities of the insurers, we were unable to account for regional differences caused by differences in the timing and the extent to which the COVID-19 pandemic influenced the local medical systems across Japan, which may be one of the important confounders. These database specifications limit the generalizability of the current results; therefore, further validation studies using nationwide claims data (*e.g.*, NDB) will be necessary to obtain a more robust conclusion.

In conclusion, our study suggests that, in Japan, the impact of the COVID-19 pandemic on ambulatory care for certain chronic neurological diseases was relatively limited during the first half of 2020 in terms of the frequency or type of outpatient visits.

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References

1. Katayama Y, Kiyohara K, Kitamura T, Hayashida S, Shimazu T. Influence of the COVID-19 pandemic on an emergency medical service system: A population-based, descriptive study in Osaka, Japan. Acute Med Surg. 2020; 7:e534.
2. Ministry of Health, Labor and Welfare. Avoid the "Three Cs". *https://www.mhlw.go.jp/content/3CS.pdf* (accessed April 2, 2021).
3. Sud A, Torr B, Jones ME, *et al.* Effect of delays in the 2-week-wait cancer referral pathway during the COVID-19 pandemic on cancer survival in the UK: A modelling study. Lancet Oncol. 2020; 21:10355-1044.
4. Japan Medical Association. Questionnaire survey on the status of medical practice management under the new coronavirus. *https://www.med.or.jp/dl-med/teireikaiken/20200610_6.pdf* (accessed April 2, 2021).
5. Ministry of Health, Labor and Welfare. Temporary measures for medical reimbursement for new coronavirus infections. (*https://www.mhlw.go.jp/content/000602230.pdf* (accessed April 2, 2021). (in Japanese)
6. Bloem BR, Dorsey ER, Okun MS. The coronavirus disease 2019 crisis as catalyst for telemedicine for chronic neurological disorders. JAMA Neurol. 2020; 77:927-928.
7. Looi MK. Covid-19: Japan declares state of emergency as Tokyo cases soar. BMJ. 2020 Apr 9; 369:m1447.
8. Wosik J, Clowse MEB, Overton R, Adagarla B, Economou-Zavlanos N, Cavalier J, Henao R, Piccini JP, Thomas L, Pencina MJ, Pagidipati NJ. Impact of the COVID-19 pandemic on patterns of outpatient cardiovascular care. Am Heart J. 2021 Jan;231:1-5. doi: 10.1016/j.ahj.2020.10.074. Epub 2020 Nov 1. PMID: 33137309; PMCID: PMC7604084.
9. Saliba-Gustafsson EA, Miller-Kuhlmann R, Kling SMR, Garvert DW, Brown-Johnson CG, Lestoquoy AS, Verano MR, Yang L, Falco-Walter J, Shaw JG, Asch SM, Gold CA, Winget M. Rapid implementation of video visits in neurology during COVID-19: Mixed methods evaluation. J Med Internet Res. 2020; 22:e24328.
10. Yang L, Brown-Johnson CG, Miller-Kuhlmann R, Kling SMR, Saliba-Gustafsson EA, Shaw JG, Gold CA, Winget M. Accelerated launch of video visits in ambulatory neurology during COVID-19: Key lessons from the Stanford experience. Neurology. 2020; 95:305-311.
11. French JA, Brodie MJ, Caraballo R, *et al.* Keeping people with epilepsy safe during the COVID-19 pandemic. Neurology. 2020; 94:1032-1037.
12. Reeves JJ, Ayers JW, Longhurst CA. Telehealth in the COVID-19 era: A balancing act to avoid harm. J Med Internet Res. 2021; 23:e24785.
13. Ministry of Health, Labor and Welfare. Study group on the review of guidelines for the appropriate implementation of online medical treatment. *https://www.mhlw.go.jp/stf/shingi/other-isei_513005_00001.html* (accessed April 2, 2021). (in Japanese)
14. Whaley CM, Pera MF, Cantor J, Chang J, Velasco J, Hagg HK, Sood N, Bravata DM. Changes in health services use among commercially insured US populations during the COVID-19 pandemic. JAMA Netw Open. 2020; 3:e2024984.
15. Zhao J, Wang Y, Fisher M, Liu R. Slower recovery of outpatient clinics than inpatient services for stroke and other neurological diseases after COVID-19 pandemic. CNS Neurosci Ther. 2020; 26:1322-1326.
16. Sakata N, Okumura Y. Thyroid function tests before prescribing anti-dementia drugs: A retrospective observational study. before press. Clin Interv Aging. 2018; 13:1219-1223.
17. Ministry of Health, Labor and Welfare. An outline of the Japanese medical system. *https://www.mhlw.go.jp/english/policy/health-medical/health-insurance/index.html* (Accessed April 2, 2021).
18. Takemura S. Sone T. Research and development on intractable & rare diseases in Japan: Contribution of the National Institute of Public Health to research program management. Journal of the National Institute of Public Health. 2019; 68:45-54.
19. Nakaoka S, Ishizaki T, Urushihara H, Satoh T, Ikeda S, Yamamoto M, Nakayama T. Prescribing pattern of anti-Parkinson drugs in Japan: A trend analysis from 2005 to 2010. PLoS One. 2014; 9:e99021.
20. Suzuki M, Arai M, Hayashi A, Ogino M. Adherence to treatment guideline recommendations for Parkinson's disease in Japan: A longitudinal analysis of a nationwide medical claims database between 2008 and 2016. PLoS One. 2020; 15:e0230213.
21. Fonferko-Shadrach B, Lacey AS, White CP, Powell HWR, Sawhney IMS, Lyons RA, Smith PEM, Kerr MP, Rees MI, Pickrell WO. Validating epilepsy diagnoses in

routinely collected data. Seizure. 2017; 52:195-198.
22. Moura LM, Price M, Cole AJ, Hoch DB, Hsu J. Accuracy of claims-based algorithms for epilepsy research: Revealing the unseen performance of claims-based studies. Epilepsia. 2017; 58:683-691.
23. Aragon TJ 2020. epitools: Epidemiology Tools. R package version 0.5-10.1. *https://CRAN.R-project.org/package=epitools* (accessed April 2, 2021).
24. Balduzzi S, Rücker G, Schwarzer G. How to perform a meta-analysis with R: A practical tutorial. Evid Based Ment Health. 2019; 22:153-160.
25. Kurita N. Association of the Great East Japan Earthquake and the Daiichi nuclear disaster in Fukushima City, Japan, with birth rates. JAMA Netw Open. 2019; 2:e187455.
26. Harada S, Uno S, Ando T, *et al.* Control of a nosocomial outbreak of COVID-19 in a university hospital. Open Forum Infect Dis. 2020; 7:ofaa512.
27. Sato K, Mano T, Iwata A, Toda T. Neuropsychiatric adverse events of chloroquine: A real-world pharmacovigilance study using the FDA Adverse Event Reporting System (FAERS) database. BioSci Trends. 2020; 14:139-143.
28. Bates D, Mächler M, Bolker B, Walker S. Fitting linear mixed-effects models using lme4. J Stat Softw. 2015; 67:1-48.
29. Xiao H, Dai X, Bradley H. Wagenaar BH, Liu F, Augusto O, Guo Y, Unger JM. The impact of the COVID-19 pandemic on health services utilization in China: Time-series analyses for 2016-2020. Lancet Reg Health West Pac. 2021; 9:1-10.
30. Bruine de Bruin W. Age differences in COVID-19 risk perceptions and mental health: Evidence from a national U.S. survey conducted in March 2020. J Gerontol B Psychol Sci Soc Sci. 2021; 76:e24-e29.
31. Al-Chalabi M, Alshaer Q, Zakarna L, Robertson J, Manousakis G, Ghannam M. The Impact of Coronavirus Disease-2019 on Outpatient Neurology. J Neurol Neurosci. 2020; 11:327.
32. Szperka CL, Ailani J, Barmherzig R, Klein BC, Minen MT, Halker Singh RB, Shapiro RE. Migraine care in the era of COVID-19: Clinical pearls and plea to insurers. Headache. 2020; 60:833-842.
33. Kelman L. Migraine changes with age: IMPACT on migraine classification. Headache. 2006; 46:1161-1171.
34. Assenza G, Lanzone J, Brigo F, Coppola A, Di Gennaro G, Di Lazzaro V, Ricci L, Romigi A, Tombini M, Mecarelli O. Epilepsy care in the time of COVID-19 pandemic in Italy: Risk factors for seizure worsening. Front Neurol. 2020; 11:737.
35. Zebenholzer K, Gall W, Wöber C. Use and overuse of triptans in Austria - a survey based on nationwide healthcare claims data. J Headache Pain. 2018; 19:34.

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