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Epidemiology of Chronic Inflammatory Demyelinating Polyneuropathy in South Korea: A Population-Based Study

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Background and Purpose We performed a population-based study to determine the prevalence and incidence of chronic inflammatory demyelinating polyneuropathy (CIDP) in South Korea using data from the Korean Health Insurance Review and Assessment Service (HIRA) database.

Methods Data recorded in the HIRA database between January 2016 and December 2020 were analyzed. The inclusion criteria in this study for patients with CIDP were a diagnostic code of G61.8 in the seventh and eighth revision of the Korean Standard Classification of Disease and a >3-month history of oral immunosuppressant use. The age-adjusted incidence rate and prevalence of CIDP in South Korea were also analyzed.

Results CIDP was newly diagnosed in 953 patients during the study period. The mean age at diagnosis was 58.36 years, and the male-to-female ratio was 1.74. The age-adjusted incidence rates were 0.22, 0.21, 0.23, 0.30, and 0.25 per 100,000 person-years in 2016, 2017, 2018, 2019, and 2020, respectively. The age-adjusted prevalence was estimated at 1.16 per 100,000 persons in 2020. Age and the Elixhauser Comorbidity Index were associated with the in-hospital mortality of patients with CIDP. Infection and cardiovascular disease (CVD) were also significantly associated with the in-hospital mortality of those patients. Acute-onset CIDP was initially diagnosed in an estimated 101 out of 953 patients with CIDP.

Conclusions The prevalence and incidence rates of CIDP in South Korea were comparable between this nationwide cohort study and previous studies. Common comorbidities such as CVD and diabetes should be appropriately monitored in patients with CIDP to prevent a poor prognosis and socioeconomic burden.

Keywords polyradiculoneuropathy, chronic inflammatory demyelinating; incidence; prevalence; epidemiology; insurance, health.

INTRODUCTION

Chronic inflammatory demyelinating polyneuropathy (CIDP) is a rare immune-mediated disorder of the peripheral nerves and nerve roots.[1] It is characterized by progressive weakness, impaired sensory function, areflexia, and limb fatigue.[2] CIDP is a long-term condition with a varying course that can be relapsing-remitting, stepwise progressive, or gradually progressive.[1,2]

A recent meta-analysis that included patients from Europe, USA, Japan, and Australia estimated the pooled crude incidence rate of CIDP to be 0.33 per 100,000 person-years, and the prevalence rate to be 2.81 per 100,000 years.[3] That meta-analysis found no significant differences in the incidence and prevalence rates of CIDP between European and non-European countries. However, there were still limitations to its epidemiological generalizability in the clinical setting of East Asia, because Japan was the only Asian country

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included among the non-European countries.

South Korea has a public medical insurance system, called the National Health Insurance Service (NHIS), which covers almost the entire population.[4,5] Under the NHIS, the Korean Health Insurance Review and Assessment Service (HIRA) evaluates medical fees, quality of care, and adequacy of medical services. It collects the data of each patient to evaluate these public services, including diagnoses, treatments, procedures, and drug prescriptions. The HIRA database has been used in several epidemiological studies on neurological disorders such as multiple sclerosis, neuromyelitis optica spectrum disorder, and Huntington's disease.[6-8] However, epidemiological studies on CIDP have not yet been conducted in South Korea. This study therefore aimed to determine the prevalence and incidence rates of CIDP in South Korea during 2016–2020 using data from the HIRA database. We also analyzed acute-onset CIDP and the risk factors for a poor prognosis in South Korean patients with CIDP.

METHODS

Characteristics of data sources

The NHIS covers approximately 98% of the South Korean population due to every resident being legally required to be covered by this scheme.[9] After the HIRA reviews NHIS claims from healthcare institutions, the NHIS reimburses these institutions for medical expenses. HIRA data were obtained from the payment claim forms generated from each inpatient or outpatient visit to a healthcare institution. The HIRA currently provides nationwide claims data to researchers during this process. HIRA claims data include age, sex, diagnoses, medical costs, procedures, drug prescriptions, and a unique anonymous number for each patient.[4,9] All healthcare institutions submit claims data to the NHIS of South Korea, including diagnosis codes classified according to the Korean Standard Classification of Disease (KCD), which is the Korean version of the International Classification of Diseases. This study was performed using the HIRA research data (M20220314875).

Statement of ethics

This study was approved and written informed consent was waived by Korea national institute for bioethics policy (No. 2022-0160-002).

Study design, population, and setting

This retrospective population-based cohort study of patients with CIDP utilized a nationwide claims database. Diagnostic codes and adjusted medication history were used to operationally define patients with CIDP. First, enrolled patients with CIDP should have a primary diagnostic code of G61.8, according to seventh (KCD-7) and eighth (KCD-8) revisions of KCD. CIDP has been specifically coded using G61.8 and differentiated from other inflammatory neuropathies since KCD-7, which officially began being used by medical institutions on January 1, 2016. South Korean medical institutions must diagnose CIDP according to the 2010 criteria of the European Federation of Neurological Associations and Peripheral Nerve Society to obtain reimbursement from the NHIS.[10] Second, enrolled patients with CIDP had to have a >3-month history of oral immunosuppressive treatment. The G61.8 code indicates CIDP and multifocal motor neuropathy (MMN) according to KCD-7 and KCD-8. The current KCD format does not provide seperate diagnostic codes for CIDP or MMN. Oral immunosuppressive agents are applied as the first-line maintenance treatment for CIDP, and regular intravenous immunoglobulin (IVIG) is considered based on the status of the patient, whereas regular IVIG is the only possible initial and maintenance treatment of MMN in the current system, in which HIRA reviews NHIS claims.[11] The inclusion criteria for patients with CIDP in this study were therefore a diagnostic code of G61.8 and a dispensing record of oral immunosuppressive treatment as a maintenance therapy for >3 months. This maintenance treatment should be adjusted after a registration of code G61.8.

Estimation of prevalence and incidence rates

The prevalence was calculated among patients from the HIRA database who met the inclusion criteria between January 1, 2016, and December 31, 2020. Furthermore, patients who only newly met the inclusion criteria during the 5-year measurement period (2016–2020) were used to calculate the annual incidence rate. Patients with codes (G61.0–61.4) that indicated disorders of the peripheral nervous system before 2016, which were modified to G61.8 after KCD-7 was established, were therefore excluded from the incidence survey (Fig. 1). The general population data used to calculate CIDP incidence and prevalence rates were obtained from the Korean Statistical Information Service.[12] The age distribution used in the age adjustment was based on the 2000–2020 standard population of the World Health Organization.[13]

Clinical characteristics and acute-onset CIDP

Patients identified as having CIDP during the 5-year study period were surveyed for their medication history, disease for hospitalization, and emergency room visits. Intensive care unit (ICU) admission and in-hospital mortality were evaluated to determine severe medical deterioration during treatment. The Elixhauser Comorbidity Index (ECI) measured the burden of comorbid diseases.[14] However, acquired

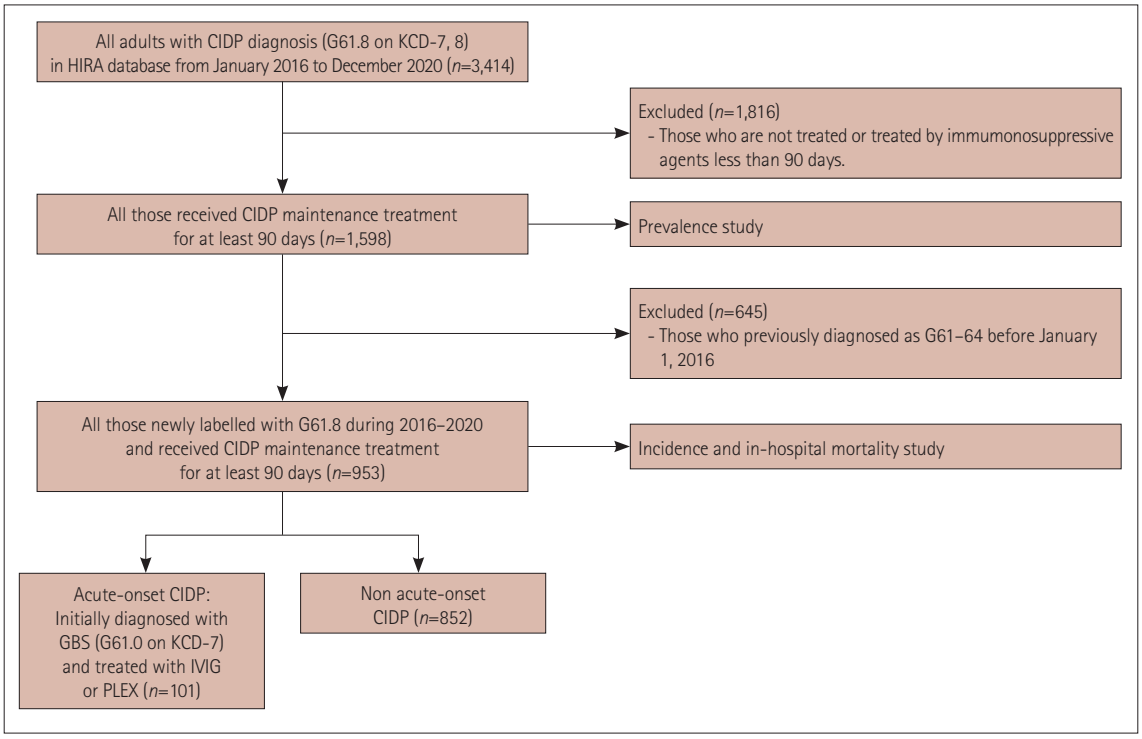

Fig. 1. Flowchart of the study population selection. CIDP, chronic inflammatory demyelinating polyneuropathy; GBS, Guillain-Barré syndrome; HIRA, Korean Health Insurance Review and Assessment Service; IVIG, intravenous immunoglobulin; KCD, Korean Standard Classification of Disease; PLEX, plasma exchange.

immunodeficiency syndrome/human immunodeficiency virus infection, drug abuse, psychoses, and depression were not included in this calculation since they were absent in the public database due to legal access restrictions for ensuring human rights. KCD-7 diagnosis codes according to ECIs are listed in Supplementary Table 1 (in the online-only Data Supplement). ECIs were categorized into four groups (scores of 0, 1, 2, and 3+) based on its distribution in our study cohort, and these categories were used in the descriptive and multivariate analyses. Patients initially diagnosed with Guillain-Barré syndrome (GBS), indicated by a diagnostic code of G61.0, and treated using IVIG or plasma exchange (PLEX), were rediagnosed with acute-onset CIDP when their diagnostic code changed to G61.8. Age at diagnosis, ECI, and the extent of clinical deterioration were compared between the acute-onset CIDP group and the other CIDP groups.

Statistical analysis

The outcomes were assessed using univariate and multivariate models. We used the Cox proportional-hazards model to examine the factors associated with in-hospital mortality. The proportional-hazards assumption for the Cox model was confirmed using the Schoenfeld residual test. The following covariates were used in the Cox model: age at diagnosis, sex, region of residence, hospital volume, and treatments, which included IVIG, oral immunosuppressants, oral or intravenous steroids, and PLEX. Age was examined as a categorical variable in 10-year groups to reduce the violation of the proportional-hazards assumption. We performed a logistic regression analysis to determine the effects of variables on the risk of ICU admission. All results are presented with 95% confidence intervals (CIs). All analyses were conducted using R software (version 4.2.0 for Windows), and $p<0.05$ was considered significant.

RESULTS

Characteristics of South Korean patients with CIDP

Between January 1, 2016, and December 31, 2020, 3,414 patients with CIDP were assigned a diagnostic code of G61.8. Among them, 1,598 were evaluated after adjusting for a >3-month history of sustained oral immunosuppressive treatment. During the study period, 953 patients with CIDP were initially assigned a diagnostic code of G61.8, whereas the remaining 645 had previously been classified using other codes (G61–G64) and then demonstrated a diagnostic code of G61.8 after January 1, 2016 (Fig. 1). Among the 953 patients with CIDP, the most common group for age at first diagnosis was 60–69 years (236 patients), followed by 50–59 years (Table 1). Furthermore, 446 (46.80%) patients were treated using ad-

Table 1. Demographic and clinical characteristics of 953 adult patients with CIDP in South Korea in the Korean HIRA database during 2016–2020

Characteristic	Value
Age at diagnosis, years	
20–29	38 (4.0)
30–39	70 (7.3)
40–49	151 (15.8)
50–59	206 (21.6)
60–69	236 (24.8)
70–79	199 (20.9)
80≤	53 (5.6)
Mean age at diagnosis (M:F), years	58.4 (58.8:57.4)
Male sex	634 (66.5)
Region of residence, capital area	542 (56.9)
Steroid treatment as initial therapy	882 (92.5)
Treatment using immunosuppressive agents*	446 (46.8)
Azathioprine	339
Mycophenolate mofetil	94
Methotrexate	35
Tacrolimus	30
Cyclosporine	15
Cyclophosphamide	5
Rituximab	5
Treatment with IVIG	314 (32.9)
Treatment with PLEX	22 (2.3)
Elixhauser Comorbidity Index	
0	69 (7.2)
1	148 (15.5)
2	188 (19.7)
3≤	548 (57.5)
History of visiting the emergency room	349 (36.6)
Common cause of emergency room visits	
Polyneuropathies and other peripheral nervous system disorders (G60–G64)	33
Intestinal infectious diseases (A00–A09)	31
Urticaria and erythema (L50–154)	17
Acute upper respiratory infections (J00–J06)	13
Other dorsopathies (M50–M54)	13
Hospitalization	787 (82.6)
Common cause of hospitalization	
Polyneuropathies and other peripheral nervous system disorders (G60–G64)	599
Influenza and pneumonia (J09–J18)	50
Cerebral palsy and other paralytic syndromes (G80–G83)	38
Other dorsopathies (M50–M54)	30
Renal failure (N17–N19)	29
ICU admission	129 (13.5)
In-hospital mortality	80 (8.4)

Data are *n* (%) or *n* values except where indicated otherwise.
*Multiple drug therapy was adjusted.
CIPD, chronic inflammatory demyelinating polyneuropathy; HIRA, Korean Health Insurance Review and Assessment Service; ICU, intensive care unit; IVIG, intravenous immunoglobulin; PLEX, plasma exchange.

ditional oral immunosuppressive agents such as azathioprine, mycophenolate mofetil, methotrexate, tacrolimus, cyclosporine, cyclophosphamide, and rituximab, with azathioprine being the most commonly administered (339 patients). IVIG and/or PLEX were administered to 336 patients. Furthermore, 548 (57.50%) patients were classified into four groups based on ECIs. The most common cause of hospitalization was peripheral nervous system disorder (599 patients), as indicated by diagnostic codes G60–G64, followed by upper respiratory infections such as influenza and pneumonia (indicated by codes J09–J18). Peripheral nervous system disorders (codes G60–G64) were also the most common cause (33 patients) in the emergency room, followed by intestinal infectious disease (codes A00–A09, 31 patients). Furthermore, 129 (13.50%) patients were treated in an ICU, and 80 (8.40%) died while receiving treatment at a medical institution.

Incidence and prevalence of South Korean patients with CIDP

The 953 patients newly diagnosed with and treated for CIDP during 2016–2020 comprised 634 males and 319 females (Table 2). Age-adjusted annual incidence rates in 2016, 2017, 2018, 2019, and 2020 were 0.22 (95% CI=0.19–0.25), 0.21 (95% CI=0.18–0.24), 0.23 (95% CI=0.20–0.26), 0.30 (95% CI=0.26–0.34), and 0.25 (95% CI=0.22–0.28) per 100,000 person-years, respectively. The male-to-female ratio ranged from 1.74 in 2020 (95% CI=1.31–2.32) to 2.35 in 2019 (95% CI=1.79–3.08). The prevalence study evaluated 1598 patients, which revealed an age-adjusted prevalence of 1.16 (95% CI=1.09–1.23) per 100,000 persons at the end of the evaluation period.

In-hospital mortality and acute-onset CIDP

The univariate hazard ratios (HRs) for age at diagnosis and ECI indicated that they were significantly associated with in-hospital mortality: 1.20 (95% CI=1.10–1.30, $p<0.001$) and 3.06 (95% CI=1.87–5.03, $p<0.001$), respectively (Table 3). Similarly, the adjusted HRs for age at diagnosis and ECI were significantly associated with in-hospital mortality in the multivariate analysis: 1.14 (95% CI=1.04–1.25, $p<0.001$) and 2.75 (95% CI=1.66–4.54, $p<0.001$), respectively. Congestive heart failure, hypertension, neurodegenerative disorders, diabetes, lymphoma, metastatic cancer, solid tumor without metastasis, and fluid and electrolyte disorders were significantly associated with the in-hospital mortality of patients with CIDP according to the ECIs (Supplementary Table 2 in the online-only Data Supplement). We also found several other common reasons for patients with CIDP in South Korea to visit and be admitted to the emergency room, such as intestinal infectious diseases, acute upper respiratory infections,

Table 2. Age-adjusted prevalence and incidence rates of CIDP in South Korea from the HIRA database during 2016–2020*

Year	Age-adjusted prevalence rate (per 100,000 persons)			Age-adjusted incidence (per 100,000 person-years)			Number of new cases			Sex ratio	
	Total	Males	Females	Total	Males	Females	Total	Males	Females	Males/females	95% CI
2016	0.70	0.87	0.54	0.22	0.27	0.17	154	100	54	1.94	1.39–2.70
2017	0.78	1.01	0.57	0.21	0.31	0.13	165	114	51	2.34	1.68–3.26
2018	0.91	1.23	0.62	0.23	0.33	0.14	189	126	63	2.10	1.55–2.84
2019	1.05	1.43	0.70	0.30	0.43	0.19	246	170	76	2.35	1.79–3.08
2020	1.16	1.55	0.81	0.25	0.32	0.19	199	124	75	1.74	1.31–2.32

*General population data obtained from the Korean Statistical Information Service[12] and age-adjusted based on the 2000–2020 standard population of the World Health Organization.[13]
CI, confidence interval; CIPD, chronic inflammatory demyelinating polyneuropathy; HIRA, Korean Health Insurance Review and Assessment Service.

Table 3. HRs for in-hospital mortality of patients with CIDP

Variable	Unadjusted HR (95% CI)	*p*	Adjusted HR (95% CI)*	*p*
Age at diagnosis, years	1.20 (1.10–1.30)	<0.001†	1.14 (1.04–1.25)	<0.001†
ECI	3.06 (1.87–5.03)	<0.001†	2.75 (1.66–4.54)	<0.001†
Sex ratio, males/females	1.03 (0.64–1.64)	0.91	0.98 (0.61–1.56)	0.92
Region of residence, capital/noncapital area	1.30 (0.83–2.05)	0.26	1.49 (0.95–2.36)	0.09
Treatment using IVIG, yes/no	1.08 (0.68–1.72)	0.73	1.06 (0.67–1.70)	0.83
Treatment using PLEX, yes/no	1.99 (0.73–5.44)	0.18	1.96 (0.69–5.56)	0.21

*After adjusting for age at diagnosis, ECI, male sex, region or residence, and IVIG and PLEX treatments; †Significance was set at $p<0.05$.
CI, confidence interval; CIPD, chronic inflammatory demyelinating polyneuropathy; ECI, Elixhauser Comorbidity Index; HR, hazard ratio; IVIG, intravenous immunoglobulin; PLEX, plasma exchange.

Table 4. Comparison of patients with acute-onset and non-acute-onset CIDP

Variable	Acute-onset CIDP (*n*=101)	Non-acute-onset CIDP (*n*=852)	*p*
Age at diagnosis, years	58.0±14.0	58.4±14.8	0.79
Elixhauser Comorbidity Index			0.66
0	8 (7.9)	61 (7.2)	
1	13 (12.9)	135 (15.8)	
2	24 (23.8)	164 (19.2)	
3≤	56 (55.4)	492 (57.7)	
Sex, male	72 (71.3)	562 (66.0)	0.34
Treatment with IVIG, yes	39 (38.6)	275 (32.3)	0.24
Treatment with PLEX, yes	6 (5.9)	16 (1.9)	0.03*
ICU admission during follow-up	13 (12.9)	116 (13.6)	0.96
In-hospital mortality during follow-up	7 (6.9)	73 (8.6)	0.71

Data are mean±SD or *n* (%) values.
*Significance was set at $p<0.05$.
CIPD, chronic inflammatory demyelinating polyneuropathy; ICU, intensive care unit; IVIG, intravenous immunoglobulin; PLEX, plasma exchange.

influenza, and pneumonia, systemic atrophies primarily affecting the central nervous system, and other bacterial diseases, which were also significantly associated with in-hospital mortality (Supplementary Table 3 in the online-only Data Supplement).

Among the 953 patients newly diagnosed with and treated for CIDP during 2016–2020, 101 were initially diagnosed with GBS (G61.0) and treated using IVIG and/or PLEX as the first-line treatment. Their diagnostic codes were then changed to G61.8 (indicating CIDP), and they were maintained using oral prednisolone or other immunosuppressive agents. There was a difference in the experience of PLEX between the acute-onset CIDP group (6 of 101 patients, 5.9%) and the other CIDP groups (16 of 852 patients, 1.9%) ($p=0.03$, Table 4). In contrast, there were no significant differences between the groups in age at diagnosis, ECI, male sex, region of residence, experience of IVIG, ICU admission, or in-hospital mortality.

DISCUSSION

During this study period, the incidence rate of CIDP in 2020 was 0.25 (95% CI=0.22−0.28) per 100,000 person-years, and the overall prevalence rate was 1.16 (95% CI=1.09−1.23) per 100,000 persons. CIDP was more prevalent in males and those aged ≥50 years. These findings were comparable to those of previous epidemiological studies performed in the United States, several European countries, and Japan.[3,15] It has been reported previously that there are no specific differences in the incidence and prevalence rates of CIDP according to race and region of residence, which was supported in the present study.

Steroids and other immunosuppressive agents are the main treatment options for South Korean patients with CIDP. Infection, cardiovascular disease (CVD), and diabetes were significantly associated with poor prognoses such as in-hospital mortality in the present study (Table 1 and Supplementary Tables 2, 3 in the online-only Data Supplement). CIDP is associated with diabetes mellitus, but the exact risk is yet to be determined.[15,16] Patients with CIDP and diabetes experience several challenges regarding their management. First, it is difficult to distinguish CIDP from concomitant diabetes and diabetic polyneuropathy.[17] Second, steroid therapy can cause and worsen diabetes, and the treatment protocol for preventing steroid-induced diabetes remains unclear.[18] Third, the present study found that uncontrolled diabetes leads to medical deterioration and poor treatment outcomes. Since steroids are a basic treatment option for CIDP, it is therefore worth emphasizing that careful management of diabetes is critical in CIDP management. Infections are a major concern in chronic disease treatment. Continuous immunomodulatory therapy can cause life-threatening opportunistic infections due to neuromuscular autoimmunity.[19] The findings of the present study indicate that reducing infection risk is a key therapeutic objective in CIDP management. The systemic atrophies that primarily affect the central nervous system (codes G10−G14) were significantly associated with in-hospital mortality among the patients with CIDP in this study. However, it is possible that the diagnostic codes were not accurately or thoroughly assigned in the clinical setting due to the relatively low likelihood of CIDP being combined with a corresponding disease.

Most CIDP symptoms require at least 2 months to reach their most-severe stage, but some patients demonstrate a time course that is difficult to distinguish from that of GBS. Acute-onset CIDP is challenging to diagnose and manage, particularly in determining steroid therapy.[20] According to previous research, 8%−16% of CIDP cases may be classified as acute-onset. This was consistent with the present study, which found that among 954 South Korean patients with CIDP, 101 (10.59%) with acute-onset CIDP were initially assigned as having GBS (G61.0) and were treated using IVIG or PLEX. Notably, the only variable that differed significantly between the acute-onset CIDP group and the other CIDP groups was the number of adjusted PLEX treatments. This was considered to reflect the characteristics and definition of acute-onset CIDP. In contrast, there were no differences in sex, comorbidities measured using the ECI, ICU admission, or in-hospital mortality. There might be no intergroup difference in the long-term clinical course.

This was the first epidemiological study that we are aware of on CIDP that used a nationwide South Korean database, and the second study overall among Asian countries. However, this study had several limitations. First, the prevalence and incidence rates of CIDP may have been overestimated since MMN, which shares the same G61.8 diagnostic code, could also have been included. However, the prevalence and incidence rates found in this study tended to be slightly lower than those in previous studies. This could be because the diagnostic standards that only included patients who received immunosuppressive agents for >3 months were stringent in this study. In addition, South Korea has a special welfare system in that the government compensates for medical expenses for rare diseases, known as the Rare Intractable Disease registry; however, the result of sufficient verification for assigning code G61.8 in each medical institution was considered. A possible bias was therefore considered to be meaningfully corrected. Second, the evaluation period was only 5 years since it only started when KCD-7 was first utilized. This might be responsible for the low prevalence and incidence rates. There is a need for follow-up investigations that focus on patients with CIDP in South Korea. Third, specific diseases, such as paraproteinemic neuropathies or neuropathies associated with anti-myelin-associated glycoprotein antibodies, may mimic or be misdiagnosed as CIDP and could not be scrutinized manually by investigators due to the limitations of the large nationwide database. However, these disorders have very low prevalence rates, and so it is thought that there was no substantial error in the overall analysis of the relatively common disease of CIDP.

In conclusion, CIDP demonstrated similar epidemiological results per population in this study regardless of region of residence or race. It is meaningful to investigate the factors associated with the treatment outcomes of patients and determine the pattern of acute-onset CIDP. Furthermore, it is crucial to monitor risk factors for diabetes and CVD and prevent infections while managing patients with CIDP to lower the socioeconomic burden. Further high-quality studies are needed to understand acute-onset CIDP and the re-

al-world tendencies of immunosuppressant administration in patients with CIDP.

Supplementary Materials

The online-only Data Supplement is available with this article at https://doi.org/10.3988/jcn.2023.0007.

Availability of Data and Material

The datasets generated or analyzed during the study are not publicly available due to restriction by HIRA but are may available from HIRA on resonable request.

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Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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