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Associations between neuromyelitis optica spectrum disorder, Sjögren's syndrome, and conditions with electrolyte disturbances

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ABSTRACT

Objective: Electrolyte disorders are among the important conditions negatively affecting the disease course of neuromyelitis optica spectrum disorder (NMOSD). Possible mechanisms may include renal tubular acidosis (RTA) accompanying Sjögren's syndrome (SS), syndrome of inappropriate antidiuretic hormone secretion (SIADH), and central diabetes insipidus (DI). Currently, the overlap profiles between these conditions remain uncertain.

Methods: This cross-sectional study collected data from the nationwide administrative Diagnosis Procedure Combination (DPC) database and evaluated the overlap profiles.

Results: Among the 28,285,908 individuals from 1203 DPC-covered hospitals, 8477 had NMOSD, 174108 had SS, 4977 had RTA, 7640 had SIADH, and 24,789 had central DI. Of those with NMOSD, 986 (12%) had SS. The odds ratio (OR) for a diagnosis of NMOSD in those with SS compared with those without was 21 [95% confidence interval (CI), 20–23]. Overlap between NMOSD and SS was seen both in males (OR, 28 [95% CI, 23–33]) and females (OR, 16 [15–17]) and was more prominent in the younger population. Among patients with SS, the prevalence of RTA was lower in patients with NMOSD compared with those without NMOSD. Patients with NMOSD showed a higher prevalence of SIADH (OR, 11 [7.5–17]; $p < 0.0001$) and DI (OR, 3.7 [2.4–5.3]; $p < 0.0001$). Comorbid SS in NMOSD was associated with a higher prevalence of DI.

Conclusions: Patients with NMOSD are likely to have SS, SIADH, and central DI. RTA in SS does not facilitate the overlap between NMOSD and SS. SS in NMOSD may predispose patients to DI.

1. Introduction

Neuromyelitis optica spectrum disorder (NMOSD) is a relapsing autoimmune-related neurological disease of the central nervous system (CNS), including the optic nerves, cerebral regions, hypothalamic regions, circumventricular organs (e.g., area postrema), and the spinal cord [1]. The disease is characterized by the presence of serum aquaporin-4-immunoglobulin G (AQP4-IgG) in the majority of patients [2–5] and is considered to be a different disease from multiple sclerosis (MS). Electrolyte disturbances occur frequently in NMOSD [6–9], which is among the primary causes of death among patients with NMOSD [10]. However, the exact profiles of the underlying conditions causing electrolyte disturbances in NMOSD remain largely uncertain. One of the conceivable causes includes comorbid renal tubular acidosis (RTA)

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among the patients with an overlap of NMOSD and primary Sjögren's syndrome (SS). Primary SS often coexists with anti-AQP4-IgG-positive NMOSD [11–13], and the relapse activity in NMOSD may increase with coexistence of SS [14–17]. RTA is a common complication of SS and presents with serum electrolyte abnormalities including hypokalemia [18,19]. A recent literature review suggested a high comorbidity rate between SS and RTA in patients with osmotic demyelination syndrome (ODS) [20]; however, the overlap profiles between NMOSD, SS, and RTA currently remain unknown. Another potential cause of electrolytic disturbances in NMOSD is the syndrome of inappropriate antidiuretic hormone secretion (SIADH) due to hypothalamic impairments [21–24]. An overlap tendency between NMOSD and central diabetes insipidus (DI) has not been reported, but a complication of central DI may be another conceivable underlying mechanism [25]. However, the prevalence of SIADH and central DI in NMOSD remain undetermined. Furthermore, it has been reported that SS could be a cause of hyponatremia based on central DI and SIADH [26,27], but the potential impact of comorbid SS on the development of SIADH and DI in NMOSD remains unknown. Therefore, the present study aimed to investigate (1) the prevalence and overlap profiles between NMOSD, SS, and RTA and (2) the impact of comorbid SS on the prevalence of SIADH and central DI in NMOSD using a large nationwide government medical record database in Japan.

2. Methods

2.1. Data source and study population

This study used the nationwide Diagnosis Procedure Combination (DPC) database in Japan. This administrative database contained data on inpatients and outpatients treated at hospitals across the country that joined the DPC-based payment system. All individuals in the country who visited the DPC-covered hospitals at least once were registered in the database, irrespective of their history of hospitalization. This payment system is governed by the Japanese Ministry of Health, Labour, and Welfare and was originally introduced in acute-care hospitals across the country in 2003 for billing purposes [28–30]. As of April 2022, >1700 hospitals nationwide, including 82 university hospitals, have joined the payment system, annually covering >30 million outpatients and 7 million inpatients across the country [31]. The DPC database contains comprehensive data regarding patient demographics, diagnoses, disease-specific disability scores or severity scores, outcomes at hospital discharge, and administered medications [31]. Diagnoses in the DPC database are registered based on the International Classification of Diseases, Tenth Revision (ICD-10) [32].

2.2. Study design

This retrospective cross-sectional observational study initially collected data of approximately 30 million individuals in Japan, who visited the DPC-covered hospitals that cooperated with this project between April 1, 2020, and March 31, 2021, with the number of hospitals exceeding 1000. Data from outpatients with no history of hospitalization were also available from this database. From the initially enrolled individuals, the presence of a medical history of NMOSD, SS, RTA, ODS, SIADH, central DI, hypernatremia, hyponatremia, hyperkalemia, and hypokalemia was recorded as binary data (Yes/No). Patients with nephrogenic DI was not included in the DI group in this study. Data on age at the last hospital visit during the study period were collected from each individual. Using these data, the overlap profiles between NMOSD, SS, and RTA and the impact of comorbid SS and/or RTA on the prevalence of SIADH or DI in NMOSD were evaluated. A flow diagram showing the study design is shown in Fig. 1.

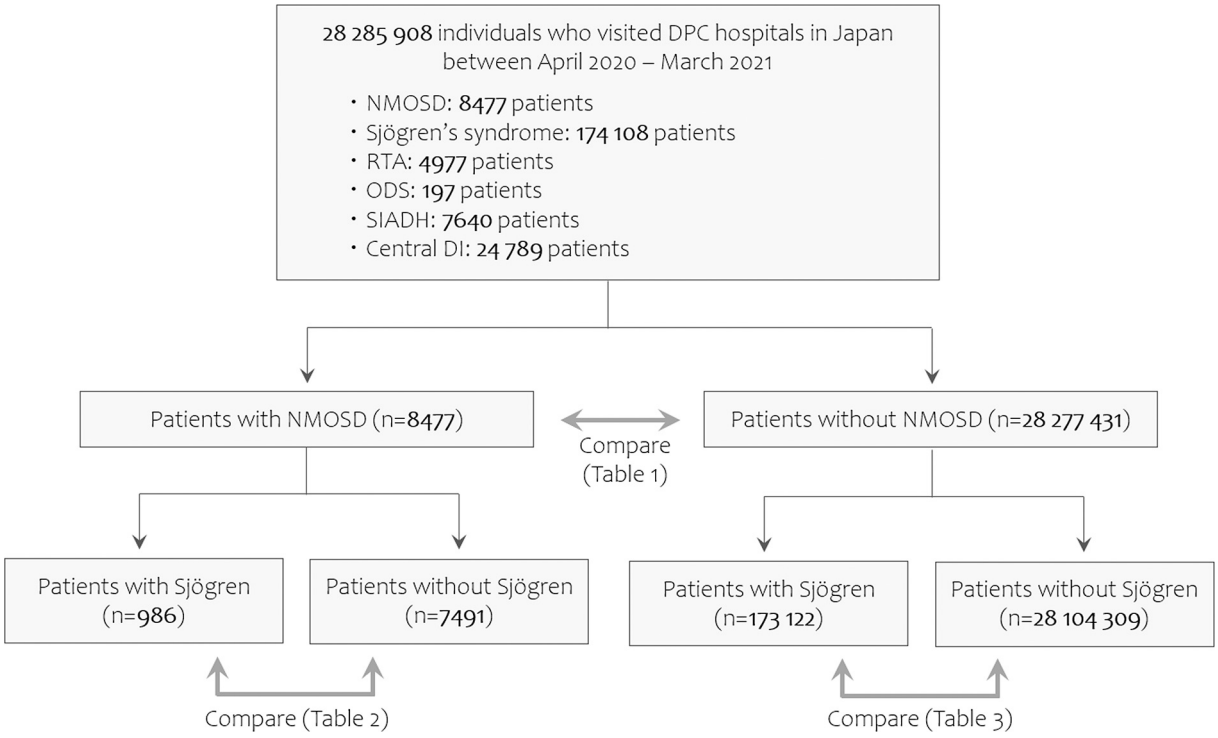

Fig. 1. Flow-diagram showing the study design.
The present study initially enrolled all individuals (n = 28,285,908) who were treated between April 2020 and March 2021 at 1203 DPC hospitals that cooperated to the present study. From these populations, the following conditions were evaluated for the prevalence and overlap profiles: NMOSD (n = 8477), SS (n = 174,108), RTA (n = 4977), ODS (n = 197), SIADH (n = 7640), and central DI (n = 24,789).
DI, diabetes insipidus; DPC, Diagnosis Procedure Combination; NMOSD, neuromyelitis optica spectrum disorder; ODS, osmotic demyelination syndrome; RTA, renal tubular acidosis; SIADH, syndrome of inappropriate antidiuretic hormone secretion; SS, Sjögren's syndrome.

2.3. Statistical analysis

The distribution of age in each population group is expressed as the median and interquartile range (IQR; 25th–75th percentiles). Comparisons of age between the groups were performed using the Mann-Whitney *U* test. Comparisons of the frequency between the groups were performed using the chi-square or Fisher's exact test based on the number of individuals in each subgroup. The unadjusted odds ratio (OR) for each evaluated complication was calculated in patients with NMOSD compared to those without NMOSD. A conditional maximum-likelihood estimate was performed for estimating the OR and 95% confidence interval (CI). Factors associated with the prevalence of SIADH, DI, or serum electrolyte abnormalities among those with NMOSD were evaluated by performing multivariable binary logistic regression analyses. The threshold for statistical significance was set at two-sided $p < 0.05$, and it was not adjusted for the number of multiple comparisons due to the exploratory nature of the present study [33]. As this study did not adjust the *p*-values for the multiple comparisons, unadjusted OR or adjusted OR as an index of effect size and 95% CI were reported in all comparisons of prevalence between two groups. The R statistical software (version 4.0.5; R Foundation, Vienna, Austria) was used for the statistical analyses [34].

2.4. Ethics

This study was approved by the institutional review boards of Tokyo Medical and Dental University (approval number: M2000–788) and Tohoku University Graduate School of Medicine (approval number: 2022–1-441). The review boards waived the requirement for written informed consent from the participants because of the anonymity of the data.

3. Results

3.1. Participant characteristics

The present study initially selected 28,285,908 individuals (including 13,359,665 males, 14,925,173 females, and 1070 of unknown sex) from a total of 1203 DPC-covered hospitals that cooperated with this project. The median (IQR) age of the overall population at the time of this cross-sectional surveillance was 64 (43–76) years. Among this population, 8477 patients (1984 males [23%], 6489 females [77%], and 4 of unknown sex) had NMOSD, 174108 individuals (30,836 males [18%], 143,259 females [82%], and 12 of unknown sex) had SS, and 4977 individuals (1735 males [35%], 3241 females [65%], and 1 of unknown sex) had RTA. The median (IQR) age at the last hospital visit during the study period was 55 (44–68) years in patients with NMOSD, 69 (54–77) years in those with SS, and 60 (38–73) years in those with RTA.

3.2. Overlap of NMOSD, SS, and RTA

The numbers of patients with NMOSD, SS, and/or RTA are shown in a Venn diagram in Fig. 2A. The combination of SS and RTA or that of SS and NMOSD was more frequent than expected in the overall population ($p < 0.0001$ for both combinations, chi-square test). Meanwhile, overlap between RTA and NMOSD was rare, reported in only six individuals (three with SS and three without SS). Of the 1664 patients with overlapping SS and RTA, 197 were males (12%) and 1467 were females (88%). Of the 986 patients with overlapping NMOSD and SS, 123 were males (12%) and 863 were females (88%). The proportion of females in the patients with overlapping NMOSD and SS was higher than that in those with non-overlapping NMOSD or SS ($p < 0.0001$ for both, chi-square test). The overlap of NMOSD and ODS was rare, and seen in only one patient among the 8477 patients with NMOSD.

Among the 174,108 patients with SS, 986 (0.57%) had NMOSD, and the remaining 173,122 did not. The median (IQR) age during the study period in the 986 patients with overlapping NMOSD and SS and those without NMOSD ($n = 173,122$) was 56 (47–68) years and 69 (54–77) years, respectively. Among the 8477 patients with NMOSD, 986 (12%) had SS, and the remaining 7491 (88%) did not, with a median (IQR) age of 56 (47–68) years and 55 (44–68) years, respectively. The distribution of age at the last hospital visit according to the combination of NMOSD and SS is shown in Fig. 2B. The peak of the age distribution in NMOSD with SS matched the peak of the age distribution in NMOSD without SS, both of which were younger than the peak in SS.

Among the 4977 patients with RTA, 1664 (33%; 197 males and 1467 females) had SS, and the remaining 3313 (67%; 1538 males, 1775 females, and 1 of unknown sex) did not. The proportion of females in the 1664 patients with overlapping RTA and SS was 88% and that in the

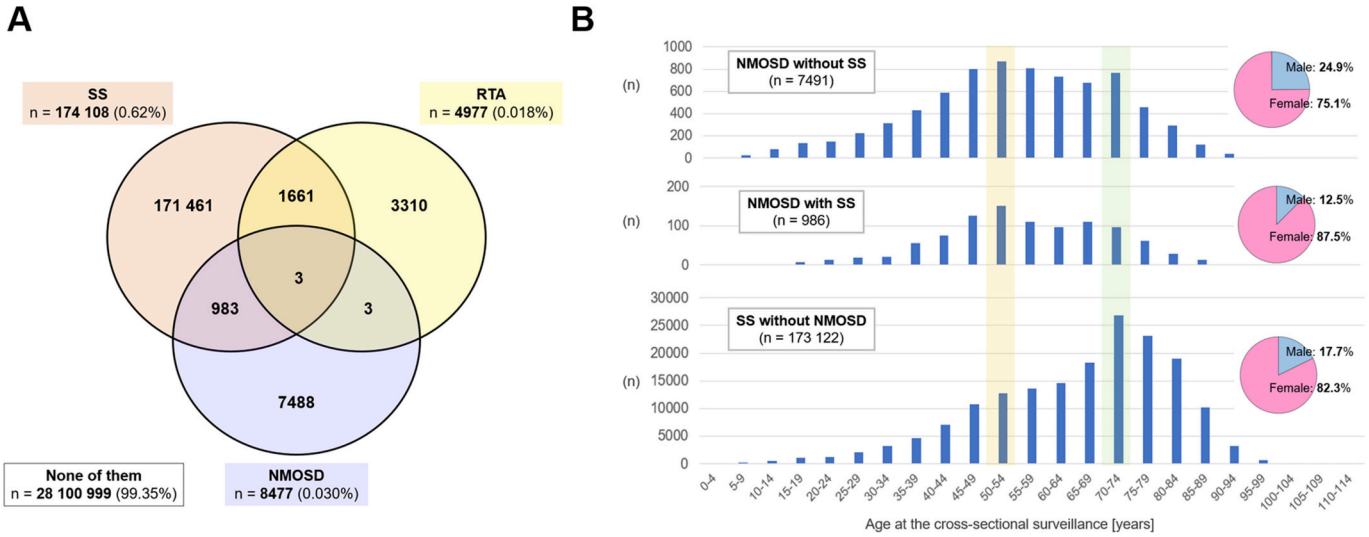

Fig. 2. Overlap profiles between NMOSD, SS, and RTA.
(A) The numbers of the participants with at least one of NMOSD, SS, and RTA are shown in this Venn diagram. Patients with NMOSD were likely to also have SS, but a coexistent RTA did not facilitate this overlap. (B) The distributions of the current age at the present cross-sectional surveillance in those with NMOSD without SS, NMOSD with SS, and SS without NMOSD are shown. The peak of the distribution in NMOSD with SS matched with that in NMOSD without SS.
NMOSD, neuromyelitis optica spectrum disorder; ODS, osmotic demyelination syndrome; RTA, renal tubular acidosis; SS, Sjögren's syndrome.

remaining 3313 patients only with RTA was 54%. The median (IQR) age at the last hospital visit was 67 (53–74) years in the former group and 55 (31–72) years in the latter.

3.3. Patients with NMOSD who had SIADH or central DI

Among the 8477 patients with NMOSD, 26 (0.31%; 3 males, 23 females) had SIADH and 27 (0.32%; 8 males, 19 females) had central DI. The proportion of females did not differ by the presence of coexisting SIADH (88% vs 77%) or central DI (70% vs 77%). The distribution of age did not differ between the 26 patients with SIADH (median: 58 [IQR: 49–70] years) and the other 8451 without SIADH (median: 55 [44–68] years). The distribution of age did not differ between the 27 patients with central DI (53 [41–67] years) and the remaining 8450 without central DI (median: 55 [44–68] years).

3.4. Overlap between NMOSD and other diseases

To evaluate whether the prevalence of NMOSD differs by the presence of other medical conditions, the unadjusted OR and its 95% CI for having NMOSD were calculated for the patients with each condition. Table 1 summarizes the results for the overall population (n = 28,285,908). A higher prevalence of SS was observed in those with NMOSD compared to those without (OR, 21; 95% CI, 20–23; $p < 0.0001$). The prevalence of NMOSD among the patients with SS was higher in females than in males (13% vs 6.0%; $p < 0.0001$, chi-square test); however, significant overlaps between NMOSD and SS were observed both in males (OR, 28; 95% CI, 23–33, $p < 0.0001$) and females (OR, 16; 95% CI, 15–17; $p < 0.0001$). The prevalence of RTA (OR, 4.0; 95% CI, 1.5–8.8; $p = 0.004$), SIADH (OR, 11; 95% CI, 7.5–17; $p < 0.0001$), and central DI (OR, 3.7; 95% CI, 2.4–5.3; $p < 0.0001$) was also higher in the 8477 patients with NMOSD compared to those without NMOSD. The presence of SS did not increase the coexistence of SIADH among NMOSD patients (0.51% vs 0.28%; $p = 0.2$), but it showed an elevated coexistence of central DI among patients with NMOSD (0.71% vs 0.27%; $p = 0.03$). For reference, among the overall population, the prevalence of central DI was higher in the 174,108 patients with SS than that for the remaining 28,111,800 patients without SS (0.19% vs 0.087%; $p < 0.0001$). Patients with NMOSD ($n = 8477$) were more likely to have hypernatremia (OR, 3.1; 95% CI, 1.4–6.0; $p = 0.0029$), hyponatremia (OR, 3.5; 95% CI, 2.8–4.2; $p < 0.0001$), and hypokalemia (OR, 3.9; 95% CI, 3.5–4.4; $p < 0.0001$).

3.5. Association between NMOSD and SS by age groups

To search for the possible mechanisms underlying the overlap between NMOSD and SS, further analyses regarding the overlap frequency between NMOSD and SS after stratifying the population by age groups were performed. The OR (95% CI) for having a diagnosis of SS in those with NMOSD compared with those without NMOSD was 57 (28–116) in 3,099,031 individuals aged <20 years, 34 (23–49) in 1,375,669 individuals aged 20–29 years, 23 (19–30) in 1,835,137 individuals aged 30–39 years, 23 (20–26) in 2,794,471 individuals aged 40–49 years, 20 (18–23) in 3,459,318 individuals aged 50–59 years, 19 (17–22) in 4,301,633 individuals aged 60–69 years, 16 (14–19) in 6,355,270 individuals aged 70–79 years, and 15 (11−20) in 5,065,379 individuals aged ≥90 years (Fig. 3). A statistical significance of $p < 0.0001$ with Fisher's exact test or chi-square test was obtained in all age groups. Moreover, despite the lower prevalence of each NMOSD or SS in younger populations, a clear tendency towards higher overlap rates between NMOSD and SS was observed in the younger age groups.

3.6. Impact of SS on other comorbidities in NMOSD

To assess the impact of SS on the relationship between NMOSD and other evaluated complications with electrolyte abnormalities, the

Table 1
Odds ratio in each evaluated condition for having NMOSD among all individuals.

	NMOSD, n (%)*		Unadjusted OR (95% CI)	P-value
	Yes (n = 8477)	No (n = 28,277,431)		
SS (n = 174,108)	986 (0.57%)	173,122 (99.43%)	21 (20−23)	<0.0001
Others (n = 28,111,800)	7491 (0.027%)	28,104,309 (99.97%)		
Males with SS†	119 (0.39%)	30,717 (99.61%)	28 (23−33)	<0.0001
Other males	1865 (0.014%)	13,326,964 (99.99%)		
Females with SS†	863 (0.60%)	142,409 (99.40%)	16 (15–17)	<0.0001
Other females	5626 (0.038%)	14,776,275 (99.96%)		
RTA (n = 4977)	6 (0.12%)	4971 (99.88%)	4.0 (1.5–8.8)	0.0043
Others (n = 28,280,931)	8471 (0.030%)	28,272,460 (99.97%)		
RTA with SS (n = 1664)	3 (0.18%)	1661 (99.82%)	6.0 (1.2–18)	0.014
Others (n = 28,284,244)	8474 (0.030%)	28,275,770 (99.97%)		
RTA without SS (n = 3313)	3 (0.091%)	3310 (99.91%)	3.0 (0.62–8.9)	0.079
Others (n = 28,282,595)	8474 (0.030%)	28,274,121 (99.97%)		
ODS (n = 197)	1 (0.51%)	196 (99.49%)	17 (0.43–96)	0.057
Others (n = 28,285,711)	8476 (0.030%)	28,277,235 (99.97%)		
SIADH (n = 7640)	26 (0.34%)	7614 (99.66%)	11 (7.5–17)	<0.0001
Others (n = 28,278,268)	8451 (0.030%)	28,269,817 (99.97%)		
Central DI (n = 24,789)	27 (0.11%)	24,762 (99.89%)	3.7 (2.4–5.3)	<0.0001
Others (n = 28,261,119)	8450 (0.030%)	28,252,669 (99.97%)		
Hypernatremia (n = 9586)	9 (0.094%)	9577 (99.91%)	3.1 (1.4–6.0)	0.0029
Others (n = 28,276,322)	8468 (0.030%)	28,267,854 (99.97%)		
Hyponatremia (n = 104,223)	107 (0.10%)	104,116 (99.90%)	3.5 (2.8–4.2)	<0.0001
Others (n = 28,181,685)	8370 (0.030%)	28,173,315 (99.97%)		
Hyperkalemia (n = 272,668)	65 (0.024%)	272,603 (99.98%)	0.79 (0.61–1.01)	0.063
Others (n = 28,013,240)	8412 (0.030%)	28,004,828 (99.97%)		
BrS (n = 19,795)‡	3 (0.015%)	19,792 (99.98%)	0.51 (0.10–1.5)	0.30
Others (n = 28,266,113)	8474 (0.030%)	28,257,639 (99.97%)		
AMG (n = 63,115)‡	13 (0.021%)	63,102 (99.98%)	0.69 (0.37–1.2)	0.21
Others (n = 28,222,793)	8464 (0.030%)	28,214,329 (99.97%)		
UCA (n = 130,890)§	24 (0.018%)	130,866 (99.98%)	0.61 (0.39–0.91)	0.018
Others (n = 28,155,018)	8453 (0.030%)	28,146,565 (99.97%)		
Hypokalemia (n = 267,108)	304 (0.11%)	266,804 (99.89%)	3.9 (3.5–4.4)	<0.0001
Others (n = 28,018,800)	8173 (0.029%)	28,010,627 (99.97%)		

AMG, adenomyomatosis of the gallbladder; BrS, Brugada syndrome; CI, confidence interval; DI, diabetes insipidus; NMOSD, neuromyelitis optica spectrum disorder; ODS, osmotic demyelination syndrome; OR, odds ratio; RTA, renal tubular acidosis; SIADH, syndrome of inappropriate antidiuretic hormone secretion; SS, Sjögren's syndrome; UCA, unruptured cerebral aneurysms.

* The shown percentages indicate those among each population with or without each disease used to calculate the OR for the overlap of NMOSD.

† After excluding individuals of unknown sex.

‡ Used as a disease control, known to have male predominance.
§ Used as a disease control, known to have female predominance.

unadjusted OR for having each condition in patients with NMOSD compared with those without NMOSD was further calculated after stratifying the population by the presence of SS. The results obtained from 174,108 patients with SS are summarized in Table 2, and the same results obtained from 28,111,800 patients without SS are summarized in Table 3. Among the 174,108 patients with SS, the prevalence of RTA was lower in the 986 patients with NMOSD compared with those without NMOSD ($n = 173,122$) (OR, 0.32; 95% CI, 0.065–0.93; $p = 0.03$). Among the 28,277,431 patients without NMOSD, SS was associated with a higher prevalence of SIADH (OR, 4.1; 95% CI, 3.5–4.8; $p < 0.0001$) and central DI (OR, 2.1; 95% CI, 1.9–2.4; $p < 0.0001$), when compared to the others without SS.

Among the 8477 patients with NMOSD, the prevalence of SIADH did not differ by the coexistence of SS ($p = 0.2$, Fisher's exact test), whereas the prevalence of central DI was higher in those with SS than in those without ($p = 0.03$). This finding was further evaluated by performing a binary logistic regression analysis among the 8477 patients with NMOSD, after adjusting for age and sex. As a result, the prevalence of SIADH in NMOSD was irrespective of age (adjusted unit OR, 1.01; 95% CI, 0.98–1.03; $p = 0.5$), sex (adjusted OR for male sex, 0.45; 95% CI, 0.13–1.5; $p = 0.2$), or comorbid SS (adjusted OR, 1.7; 95% CI, 0.62–4.4; $p = 0.3$). Meanwhile, the prevalence of central DI in NMOSD was associated with comorbid SS (adjusted OR, 2.9; 95% CI, 1.2–7.0; $p = 0.02$), whereas it was irrespective of age (adjusted unit OR, 0.99; 95% CI, 0.97–1.01; $p = 0.3$) or sex (adjusted OR for male sex, 1.5; 95% CI, 0.65–3.5; $p = 0.3$). For reference, among the 28,277,431 individuals without NMOSD, SS was associated with a higher prevalence of SIADH (OR, 4.1; 95% CI, 3.5–4.8; $p < 0.0001$) and DI (OR, 2.1; 95% CI, 1.9–2.4; $p < 0.0001$).

4. Discussion

In this study, we evaluated the demographic data and overlap profiles of patients with NMOSD, SS, and RTA using the nationwide administrative large DPC database in Japan. One of the primary objectives of this study was to clarify the degree of overlap between NMOSD and SS in the overall population. The results indicated that the prevalence of NMOSD in patients with SS was approximately 20 times higher than that in patients without SS. Overlap between NMOSD and SS was observed in both sexes, and it was more remarkable in the younger age groups. Meanwhile, the accompanying RTA in SS did not enhance the overlap between SS and NMOSD. Rather, it seemed to reduce the coexistence of NMOSD and SS, which was consistent with the findings of a previous study conducted in China [35]. These findings suggest that serum electrolytic imbalance or acidosis may not be among the mechanisms linking NMOSD and SS. A possible explanation for the linkage between NMOSD and SS may be the cross-reaction of antibodies against different aquaporins (AQPs) in these two diseases [36]. In NMOSD, serum anti-AQP4 antibodies can be detected in approximately 60–80% of the patients [2–4], whereas anti-AQP1, AQP5, AQP8, and AQP9 antibodies have been detected with unknown frequencies in the sera of patients with SS [37–39]. Among these AQP isoforms, AQP5 has been confirmed to be highly expressed in the exocrine glands like salivary and lacrimal glands; AQP5 disturbances may trigger clinical manifestations based on decreased water secretion from the exocrine glands [40–42]. AQP4 is the most well-known protein expressed in the CNS, especially the astrocyte foot process, but other isoforms, including AQP1, 3, 5, 8, and 9, have also been reported to be expressed in glial cells and other CNS components [43]. Currently, there is limited evidence about the presence and prevalence of serum anti-AQP antibodies other than anti-AQP4 in patients with NMOSD [44]. Future studies evaluating the presence of antibodies against AQPs other than AQP4 in patients with NMOSD or a potential cross-reactivity of anti-AQP4 with AQPs other than AQP4 may provide some insights into the mechanism underlying the overlap between NMOSD and SS.

Age groups	(n)	Prevalence of SS [%]		OR (95% CI)	*P*-values
		NMOSD	Non-NMOSD		
0–19 years	3 099 031	3.3 %	0.059 %	57 (28 - 116)	< 0.0001
20–29 years	1 375 669	7.6 %	0.24 %	34 (23 - 49)	< 0.0001
30–39 years	1 835 137	9.2 %	0.43 %	23 (19 - 30)	< 0.0001
40–49 years	2 794 471	13 %	0.63 %	23 (20 - 26)	< 0.0001
50–59 years	3 459 318	14 %	0.76 %	20 (18 - 23)	< 0.0001
60–69 years	4 301 633	13 %	0.76 %	19 (17 - 22)	< 0.0001
70–79 years	6 355 270	11 %	0.79 %	16 (14 - 19)	< 0.0001
≥ 80 years	5 065 379	9 %	0.66 %	15 (11 - 20)	< 0.0001

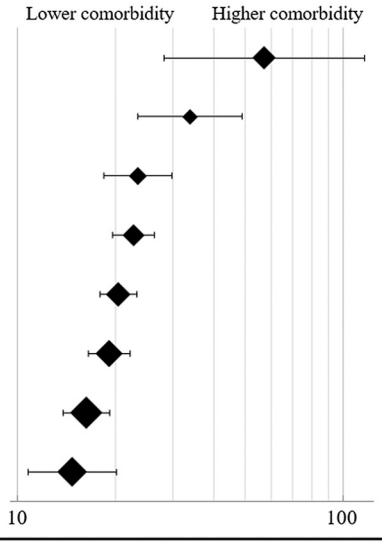

Fig. 3. Odds ratios of having both NMOSD and SS by age group.
The calculated ORs and 95% CIs (error bars) of having both NMOSD and SS in each age group are shown in the table. Each diamond represents the number of individuals in each age group. The X-axis is log-transformed. A significant overlap between NMOSD and SS was confirmed in all age groups, but the comorbidity was higher in the younger age groups.
CI, confidence interval; OR, odds ratio; NMOSD, neuromyelitis optica spectrum disorder; SS, Sjögren's syndrome.

Table 2
Odds ratio in each evaluated condition for having NMOSD among the 174,108 patients with SS.

	NMOSD, n (%)*		Unadjusted OR (95% CI)	P-value
	Yes (*n* = 986)	No (n = 173,122)		
RTA (n = 1664)	3 (0.18%)	1661 (99.82%)	0.32 (0.065–0.93)	0.031
Others (*n* = 172,444)	983 (0.57%)	171,461 (99.43%)		
ODS (n = 3)	1 (33.33%)	2 (66.67%)	88 (1.5–1.7E+3)	0.017
Others (n = 174,105)	985 (0.57%)	173,120 (99.43%)		
SIADH (*n* = 193)	5 (2.59%)	188 (97.41%)	4.7 (1.5–11)	0.0051
Others (n = 173,915)	981 (0.56%)	172,934 (99.44%)		
Central DI (*n* = 330)	7 (2.12%)	323 (97.88%)	3.8 (1.5–8.0)	0.0030
Others (n = 173,778)	979 (0.56%)	172,799 (99.28%)		
Hypernatremia (*n* = 57)	0 (0.00%)	57 (100.0%)	0.0 (0.0–12)	>0.99
Others (n = 174,051)	986 (0.57%)	173,065 (99.43%)		
Hyponatremia (*n* = 1480)	15 (1.01%)	1465 (98.99%)	1.8 (1.01–3.0)	0.034
Others (n = 172,628)	971 (0.56%)	171,657 (99.44%)		
Hyperkalemia (*n* = 2943)	6 (0.20%)	2937 (99.80%)	0.35 (0.13–0.78)	0.0042
Others (*n* = 171,165)	980 (0.57%)	170,185 (99.43%)		
Hypokalemia (*n* = 5871)	67 (1.14%)	5804 (98.86%)	2.1 (1.6–2.7)	<0.0001
Others (*n* = 168,237)	919 (0.55%)	167,318 (99.45%)		

CI, confidence interval; NMOSD, neuromyelitis optica spectrum disorder; ODS, osmotic demyelination syndrome; OR, odds ratio; RTA, renal tubular acidosis; SS, Sjögren's syndrome.
* The shown percentages indicate those among each population with or without each disease used to calculate the OR for the overlap of NMOSD.

Table 3
Odds ratio in each evaluated condition for having NMOSD among the 28,111,800 without SS.

	NMOSD, n (%)*		Unadjusted OR (95% CI)	P-value
	Yes (*n* = 7491)	No (*n* = 28,104,309)		
RTA (n = 3313)	3 (0.091%)	3310 (99.91%)	3.4 (0.70–10)	0.060
Others (n = 28,108,487)	7488 (0.027%)	28,100,999 (99.97%)		
ODS (*n* = 194)	0 (0.00%)	194 (100.0%)	0.0 (0.0–72)	>0.99
Others (n = 28,111,606)	7491 (0.027%)	28,104,115 (99.97%)		
SIADH (*n* = 7447)	21 (0.28%)	7426 (99.72%)	11 (6.6–16)	<0.0001
Others (n = 28,104,353)	7470 (0.027%)	28,096,883 (99.97%)		
Central DI (n = 24,459)	20 (0.082%)	24,439 (99.92%)	3.1 (1.9–4.8)	<0.0001
Others (n = 28,087,341)	7471 (0.027%)	28,079,870 (99.97%)		
Hypernatremia (*n* = 9529)	9 (0.094%)	9520 (99.91%)	3.6 (1.6–6.7)	0.0013
Others (n = 28,102,271)	7482 (0.027%)	28,094,789 (99.97%)		
Hyponatremia (*n* = 102,743)	92 (0.090%)	102,651 (99.91%)	3.4 (2.7–4.2)	<0.0001
Others (n = 28,009,057)	7399 (0.026%)	28,001,658 (99.97%)		
Hyperkalemia (*n* = 269,725)	59 (0.022%)	269,666 (99.98%)	0.82 (0.62–1.1)	0.14
Others (n = 27,842,075)	7432 (0.027%)	27,834,643 (99.97%)		
Hypokalemia (*n* = 261,237)	237 (0.091%)	261,000 (99.91%)	3.5 (3.0–4.0)	<0.0001
Others (n = 27,850,563)	7254 (0.026%)	27,843,309 (99.97%)		

CI, confidence interval; NMOSD, neuromyelitis optica spectrum disorder; ODS, osmotic demyelination syndrome; OR, odds ratio; RTA, renal tubular acidosis; SS, Sjögren's syndrome.
* The shown percentages indicate those among each population with or without each disease used to calculate the OR for the overlap of NMOSD.

This study also aimed to determine the prevalence of SIADH and DI in patients with NMOSD and to estimate the impact of comorbid SS on the development of these complications in NMOSD. The results of the present study demonstrated that patients with NMOSD were more likely to experience SIADH, DI, hyponatremia, hypernatremia, and hypokalemia. In addition to the possible influence of administered medications, SIADH (OR = 11) and DI (OR = 3.7) might contribute to the higher prevalence of electrolytic abnormalities in NMOSD [45,46]. Comorbid SS did not influence the prevalence of SIADH among patients with NMOSD, whereas it was associated with a slightly elevated prevalence of DI in this population. To determine the relationship between NMOSD, SS, SIADH, DI, and serum electrolyte abnormalities, additional studies with longitudinal follow-up of data from a large number of patients with NMOSD are required.

One finding that should be discussed is the higher prevalence of hyponatremia among NMOSD patients compared to those without NMOSD, which appeared to be difficult to explain as an adverse effect of oral corticosteroids. Among the 8477 patients with NMOSD, 107 had hyponatremia. Among these 107 patients with NMOSD and hyponatremia, 15 (14%) had SS, 15 (14%) had SIADH, and 2 (1.9%) had central DI. There was no patient with RTA. In other words, 92 (86%) of the 107 patients had neither SIADH nor RTA, and other mechanisms should be sought to explain the hyponatremia. Possible theories may include the occurrence of cerebral salt-wasting syndrome in NMOSD or the presence of overlooked cases with SIADH [21]. In addition to cerebral lesions, spinal lesions have the potential to cause salt-wasting as a result of kidney dysfunction in retaining sodium ions [47]. Because urine osmolarity and sodium levels were not available in this study, the validity of these theories could not be determined. The findings of this study may advocate the importance of checking for excessive urine sodium in patients with NMOSD who have hyponatremia that cannot be explained otherwise. Another notable finding in this study was that SS and NMOSD are more likely to overlap in younger age groups. This finding implied that the overlap is not an aging-related coincidental co-occurrence between two independent diseases. Rather, these two diseases could share common mechanisms existing from the earlier years of life. Established common characteristics between SS and NMOSD include the female sex and the peak of onset in middle ages, but these factors are not enough to explain the higher overlap rate between SS and NMOSD in younger age groups. Other factors like hyperactive immune responses or immune cross-reactivity between different AQP isoforms are needed to explain the finding.

This study has several limitations. First, the present study did not evaluate the use of relapse prevention treatments that might cause serum electrolytic abnormalities, including oral prednisolone, immunosuppressants, and many other medications for symptomatic management. Therefore, the contribution of therapeutic interventions to the prevalence of electrolytic abnormalities in patients with NMOSD remains unknown in this study. Second, the DPC database could not identify patients who were treated at two or more different hospitals for the same disease between April 2020 and March 2021 because of reasons such as house moving. However, we used a single-year study period to minimize the risk of double-counting those who could overlap between different hospitals because house moving is mostly done between

March and April in Japan. Therefore, the risk of counting the same individual multiple times was minimized as much as possible in this study. Third, the nationwide DPC database did not include data regarding the presence of serum disease-specific antibodies, such as anti-AQP4 or anti-myelin oligodendrocyte glycoprotein (MOG) antibodies [1]. Currently, a higher prevalence of comorbid SS has been reported only in those with anti-AQP4 antibodies and not in those with anti-MOG antibody-associated disorder, double-seronegative NMOSD, or MS. Moreover, the evaluated individuals were those who visited the DPC-covered hospitals at least once, and people who visited non-DPC hospitals or healthy individuals who had never visited the hospitals were not included in the database. Therefore, the actual value of the unadjusted OR of SS for anti-AQP4 antibody-positive NMOSD might differ from the OR obtained in this study. Finally, the time course between NMOSD and SIADH, DI, or electrolytic abnormalities was not evaluated in this study. It seems reasonable to think that SS and NMOSD could have some unknown common disease mechanisms, whereas SIADH and DI in NMOSD could be secondarily caused by cerebral NMOSD lesions involving the hypothalamus. Further studies with more detailed data on the clinical course of patients with NMOSD are needed to determine the temporal course of the onset of NMOSD, SS, SIADH, and DI.

5. Conclusions

NMOSD and SS were likely to coexist, with an unadjusted OR >20. However, the coexistence of RTA with SS was not associated with a higher prevalence of NMOSD. An overlap between NMOSD and SS was seen in both sexes, and it was more remarkable in younger populations. Patients with NMOSD were likely to show a higher prevalence of SIADH and central DI and experience serum electrolyte abnormalities. Studies with detailed data regarding the chronological time course of the onset of each condition and the start of medications affecting the serum electrolyte levels are needed to elucidate the relationships between NMOSD, SS, and other conditions related to serum osmotic and electrolytic disturbances.

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Author contributions

TA and PS designed and conceptualized the study. KT, K. Fushimi, K. Fujimori played major roles in the acquisition of data. TA, KT, and PS analyzed the data. K. Fushimi, TI, K. Fujimori, NY, IN, K. Fujihara, MA supervised the process of the study. All authors contributed to interpret the data, and critically review and revised the manuscript.

Data availability

To protect the privacy of the participants and agreements with the cooperating hospitals, individual level data cannot be shared openly or shared with third parties. However, deidentified population-level data summary supporting the findings of this study, such as the number of individuals in each subgroup, are available from the corresponding author to qualified investigators upon reasonable requests.

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