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Impact of Dysmagnesemia on Atrial Fibrillation in Maintenance Hemodialysis Patients: A Nationwide Study

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Keywords
Serum magnesium · Atrial fibrillation · Dysmagnesemia · Hemodialysis

Abstract

Introduction: The dose-response relationship between serum magnesium (sMg) and atrial fibrillation (AF) and the contribution of dysmagnesemia to AF among hemodialysis patients remain unknown. Hence, we examined the dose-response correlation between sMg and AF and estimated the extent of the contribution of dysmagnesemia to AF in this population. ***Methods:*** This was a nationwide cross-sectional study on the Japanese Society for Dialysis Therapy registry, also known as Japanese Renal Data Registry (JRDR), encompassing a nationwide population of dialysis centers, as of the end of 2019. Eligible participants were adult patients undergoing hemodialysis three times per week. The main exposure was sMg, categorized into seven categories (≤1.5, >1.5–≤2, >2–≤2.5, >2.5–≤3, >3–≤3.5, >3.5–≤4, and ≥4.0 mg/dL). The outcome was AF reported by dialysis facilities. The independent contribution to AF was assessed via logistic regression to generate population-attributable fractions, assuming a causal relationship between sMg and AF. ***Results:*** Total 165,926 patients from 2,549 facilities were investigated. AF prevalence was 7.9%. Compared with the reference (>2.5–≤3 mg/dL), lower sMg was associated with increased AF (adjusted odds ratios (ORs) (95% confidence interval, CI) of 1.49 (1.19–1.85), 1.24 (1.17–1.32), and 1.11 (1.06–1.16) for sMg of ≤1.5, >1.5–≤2.0, and >2.0–≤2.5 mg/dL categories, respectively). Elevated sMg was associated with fewer AF (adjusted OR 0.87 [95% CI, 0.79–0.96] for sMg of >3.0–≤3.5 mg/dL). The adjusted population-attributable fraction of lower sMg and higher and lower sMg for AF was 7.4% and 6.9%, respectively. An association did indeed

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exist between lower sMg and AF, with the lowest percentages of AF at sMg levels above the reference range for the general population. ***Conclusion:*** Dysmagnesemia may be an important contributor to AF among adult hemodialysis patients. Further, longitudinal studies are warranted to determine whether sMg correction reduces the AF incidence.

Introduction

Atrial fibrillation (AF) is common in maintenance hemodialysis patients. The importance of AF in dialysis patients is highlighted by a 1.5-fold higher incidence rate compared to the general population [1], a 3-fold increase in prevalence in the USA from 1992 to 2006, and the associated increased mortality [2]. While common risk factors have been described between chronic kidney disease and AF, including age, obesity, and cardiovascular disease [3], risk factors for AF associated with chronic kidney disease and dialysis treatment are not fully understood.

Because of the concern about several effects of magnesium on the cardiac conduction system, the possibility of an increased risk of AF with hypomagnesemia (below 1.77 mg/dL of serum magnesium [sMg]) has been demonstrated in the general population by the Framingham study [4]. In contrast, a positive correlation was found between sMg (including a normal range of less than 2.3 mg/dL) and AF among hemodialysis patients [5]. Determining a valid and precise dose-response relationship between sMg and AF may be helpful to understand the threshold value of sMg to reduce AF among hemodialysis patients, who are susceptible to disturbances in magnesium homeostasis.

Hence, we examined the dose-response correlation between sMg and AF using data from the Japanese Renal Data Registry (JRDR), which encompasses a nationwide population of dialysis centers. We also estimated the extent of the contribution of dysmagnesemia to AF in this population.

Methods

Study Design

This was a nationwide cross-sectional study of dialysis facilities across Japan, using a database from the JRDR collected at the end of 2019. The Japanese Society for Dialysis Therapy (JSDT) conducts a survey of all dialysis units in Japan at the end of every year. Details on the JRDR have been published previously [6]. The response rate in 2019 was 98.3% on facility basis and 94.5% on patient basis.

Participants

The inclusion criteria were as follows: participants (1) on hemodialysis (including hemodiafiltration and hemofiltration) three times a week as of the end of 2019 and (2) age ≥20 years. The exclusion criteria were as follows: participants with (1) missing sMg and AF data, (2) implausible data in real-life or apparent errors (e.g., sMg <0.5 or >5 mg/dL, height <120 or ≥200 cm, body weight <20 or ≥200 kg, body mass index [BMI] > 50 kg/m^2, ultrafiltration volume [pre-dialysis weight – post-dialysis weight] >10 kg, intradialytic weight gain [possible fluid administration during dialysis] >5 kg, or pre-dialysis diastolic blood pressure greater than the pre-dialysis systolic blood pressure).

Exposure, Outcome, and Covariates

The main exposure was pre-dialysis sMg level, which was divided into seven categories (≤1.5, >1.5–≤2, >2–≤2.5, >2.5–≤3, >3–≤3.5, >3.5–≤4, and ≥4.0 mg/dL). This categorization was defined a priori based on several reports that a minimum of five groups are required to properly analyze nonlinear relationships since both low and high sMg levels should cause adverse events from a pathophysiological perspective [5, 7]. The outcome variable was the presence of AF. The reporting of AF to dialysis facilities was requested by the JSDT and was based on the results of a resting 12-lead electrocardiography (ECG) performed at the facilities. A directed acyclic graph (DAG) was created to characterize the relationships among sMg, AF, and other essential variables. The model was based on the best available evidence or expertise in the nephrology area when evidence was not available. The final DAG model was reviewed and approved by the investigators (T.T., N.K., and N.J.; online suppl. Fig. 1; for all online suppl. material, see https://doi.org/10.1159/000536595). Based on the DAG, the established analysis rule with the Dagitty web application (www.dagitty.net) was used to determine whether a given variable should be considered a confounder, collider, or neither a confounder nor a collider [8]. In addition, this rule was used to determine a minimally sufficient adjustment set of variables for regression to estimate the total effects of sMg on AF [9]. This set of variables included age, sex, blood pressure, smoking, diabetes, ischemic heart disease (IHD), ultrafiltration volume, and treatment time. We considered these variables and BMI as covariates.

Statistical Analysis

All statistical analyses were conducted using Stata version 15.0 (Stata Corp., College Station, TX, USA). Patient characteristics were described overall and by the seven categories of sMg levels. Next, odds ratios (ORs) were estimated by fitting a series of logistic regression models to examine the association between sMg and AF. We used >2.5–≤3 mg/dL as the reference range for sMg based on several reports that proposed a higher than-normal reference [5, 10]. ORs were estimated using three models: an unadjusted model, an age- and sex-adjusted model, and a model adjusted for all covariates (i.e., an extended model). Next, we estimated the population-attributable fraction from the cross-sectional data to quantify the potential contribution of sMg to AF, assuming the causal relationship between sMg and AF. For the estimation of the population-attributable fraction, we employed a scenario-comparison approach with Stata's punaf command based on the extended model described above [9]. Population-attributable fractions of sMg were estimated for the scenario in which all patients' sMg fell into the 2.5–3.0 mg/dL category and for that

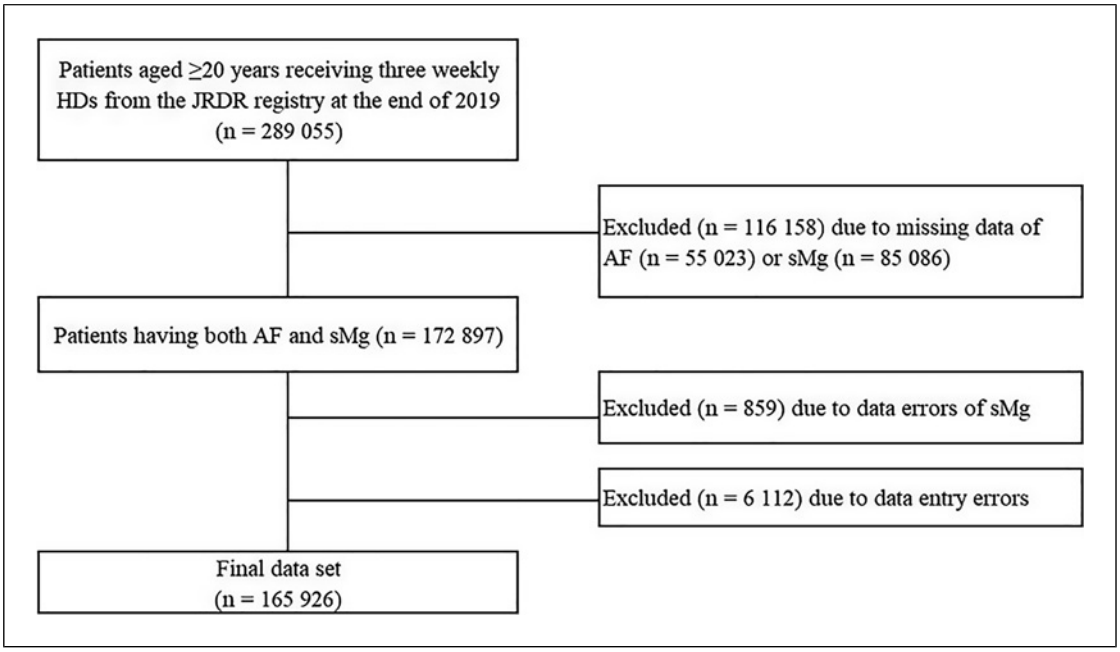

Fig. 1. Patient flowchart. HDs, hemodialysis; JRDR, Japanese Renal Data Registry; AF, atrial fibrillation; sMg, serum magnesium.

in which the patients' sMg below the 2.5–3.0 mg/dL category fell into the 2.5–3.0 mg/dL category. To interpret the magnitude of the population-attributable fraction, we also estimated the respective fraction of IHD to AF. Multiple imputations with chained equations were applied to address missing covariates, assuming that the missing mechanism was at random. Twenty imputations were performed, and the estimates were combined based on Rubin's rule [11].

Results

Characteristics of Patients

A total of 289,055 patients aged 20 years or older on hemodialysis three times a week were identified (Fig. 1). Of these, 116,158 patients with missing AF (n = 55,023) or sMg (n = 85,086) values and implausible values for sMg (n = 859) or covariates (n = 6,112) were excluded. Eventually, 165,926 patients from 2,549 dialysis centers were included in the analysis.

The characteristics of the patients are presented in Table 1. Their mean age was 69 years, and mean dialysis duration was 8.2 years. Of all patients, 65.8% were men, 51.9% had diabetes mellitus, and 26.5% had IHD. The prevalence of AF was 7.9%.

Mean age was lower in the sMg of >2.5–≤3.0 mg/dL and >3.0–≤3.5 mg/dL categories, diabetes mellitus was less common in the sMg of >2.0–≤2.5 mg/dL and >2.5–≤3.0 mg/dL categories, and IHD was less common in the sMg of >3.0–<3.5 mg/dL and >3.5–<4.0 mg/dL categories. Like IHD, AF was less common in the sMg >3.0–≤3.5 mg/dL and >3.5–≤4.0 mg/dL categories. AF was most common in the sMg ≤1.5 mg/dL category, followed by the sMg >1.5–≤2.0 mg/dL category (11.5% and 10.3%, respectively).

Associations between sMg and Prevalent AF

The correlation between sMg and AF is shown in Figure 2. In the unadjusted model, the OR for prevalent AF increased with a decrease in sMg; the greatest OR was observed in the sMg of ≤1.5 mg/dL category (OR 1.81), whereas the lowest OR was in the sMg of >3.0–≤3.5 mg/dL category (OR 0.80). We did not find significantly higher ORs for prevalent AF in the categories of sMg >3.5 mg/dL.

The magnitudes of these ORs were incrementally attenuated when adjusted for age, sex, and all the covariates; however, the presence and direction of the correlation were unchanged. Adjusted ORs based on the extended model were 1.49 (95% confidence interval [CI], 1.19–1.85), 1.24 (95% CI, 1.17–1.32), 1.11 (95% CI, 1.06–1.16), and 0.87 (95% CI, 0.79–0.96) for the sMg of ≤1.5 mg/dL, >1.5–≤2.0 mg/dL, >2.0–≤2.5 mg/dL, and >3.0–≤3.5 mg/dL categories, respectively (Table 2).

Table 1. Characteristics of patients separated based on the sMg level (n = 165,926)

Demographics	sMg levels (in mg/dL)							Total
	≤1.5 (n = 845)	>1.5–≤2.0 (n = 20,498)	>2.0–≤2.5 (n = 79,076)	>2.5–≤3.0 (n = 52,724)	>3.0–≤3.5 (n = 10,278)	>3.5–≤4.0 (n = 1,847)	>4.0 (n = 658)	(n = 165,926)
Age, years[a]	70 (11.4)	72 (11.6)	70.1 (12)	67 (12.4)	65.3 (12.9)	68.9 (12.6)	71.1 (12.5)	69 (12.3)
Men, n (%)	591 (69.9)	13,661 (66.7)	52,581 (66.5)	34,379 (66.5)	6,549 (63.7)	1,082 (63.7)	335 (50.9)	109,178 (65.8)
Vintage, years[a]	6.2 (7.4)	7.4 (7.9)	8.2 (8)	8.6 (7.7)	8.6 (7.3)	8.3 (7.3)	8.3 (7.5)	8.2 (7.8)
Missing, n		15	47	27	5	2	5	101
Diabetes, n (%)	420 (52.3)	10,264 (52.5)	38,832 (51.2)	26,070 (51.2)	5,496 (55.7)	1,043 (55.7)	361 (57)	82,486 (51.9)
Missing, n	42	944	3,288	2,107	406	60	25	6,872
BMI[a], kg/m^2	21.7 (4.3)	21.9 (4.4)	22 (4.2)	22.1 (4.1)	21.8 (4.1)	20.9 (3.9)	20.8 (4.3)	22 (4.2)
Current smoker, n (%)	107 (14.2)	1,984 (10.9)	7,421 (10.5)	5,413 (10.5)	1,079 (11.7)	127 (11.7)	38 (6.5)	16,169 (10.9)
Missing, n	89	2,350	8,118	5,416	1,055	169	73	17,270
IHD, n (%)	241 (30.3)	6,019 (31.6)	20,306 (27.5)	11,832 (27.5)	2,076 (21.8)	433 (21.8)	153 (25.3)	41,060 (26.5)
Missing, n	50	1,433	5,253	3,491	742	114	52	11,135
SBP, mm Hg[a]	145.4 (26)	148.3 (24.9)	151.2 (24.2)	153.2 (24.1)	154 (24.7)	150.7 (26)	148.6 (25.6)	151.6 (24.4)
Missing, n	10	125	440	287	46	7	0	915
UFR, L/h[a]	0.56 (0.28)	0.57 (0.24)	0.6 (0.23)	0.64 (0.23)	0.64 (0.25)	0.57 (0.25)	0.53 (0.26)	0.61 (0.24)
Ultrafiltration volume, L[a]	2.2 (1.1)	2.3 (1)	2.4 (1)	2.6 (1)	2.6 (1.1)	2.3 (1)	2.1 (1.1)	2.5 (1)
Treatment time, min[a]	232.7 (32.3)	240.3 (33.1)	243.6 (32.4)	245.3 (32.6)	243.6 (32.8)	239.2 (34.8)	233.6 (35.6)	243.6 (32.7)
AF, n (%)	97 (11.5)	2,103 (10.3)	6,642 (8.4)	3,517 (8.4)	559 (5.4)	133 (5.4)	54 (8.2)	13,105 (7.9)

BMI, body mass index; IHD, ischemic heart disease; SBP, systolic blood pressure; UFR, ultrafiltration rate; AF, atrial fibrillation.
[a]Means (SD) are presented for continuous variables.

Population-Attributable Fraction for AF

Population-attributable fraction analysis demonstrated that if both lower (≤1.5, >1.5–≤2.0, >2.0–≤2.5 mg/dL) and higher (>3.0–≤3.5, >3.5–≤4.0, ≥4.0 mg/dL) sMg categories had been corrected to reference levels, the estimated proportion of AF that could potentially have been prevented was 6.9% (95% CI, 4.3–9.3) (Table 3).

Ad hoc analysis demonstrated that if lower (≤1.5, >1.5–≤2.0, >2.0–≤2.5 mg/dL) sMg categories had been corrected to reference levels (with all other parameters remaining the same), the estimated population-attributable fraction was 7.4% (95% CI, 5.1–9.7) (Table 3). Additional ad hoc analysis showed that the estimated population-attributable fraction attributable to IHD was 10.8% (95% CI, 9.7–12.0).

Discussion

The present study, for the first time, shows a dose-response relationship for the increased prevalence of AF with a sMg of ≤1.5 mg/dL, lower than the normal range in the general population (>2.0–≤2.5 mg/dL). In the Framingham Heart study involving the general population, the range of sMg associated with the incidence of AF was <1.77 mg/dL [4]. In sizable general population studies by Markovits et al. [12] and Misialek et al. [13] (the atherosclerosis risk in communities [ARIC] study), the range of sMg associated with the increasing incidence of AF was <1.9 mg/dL. Only the mineral and bone disorders outcomes study for Japanese CKD stage 5D Patients (MBD-5D) study involving

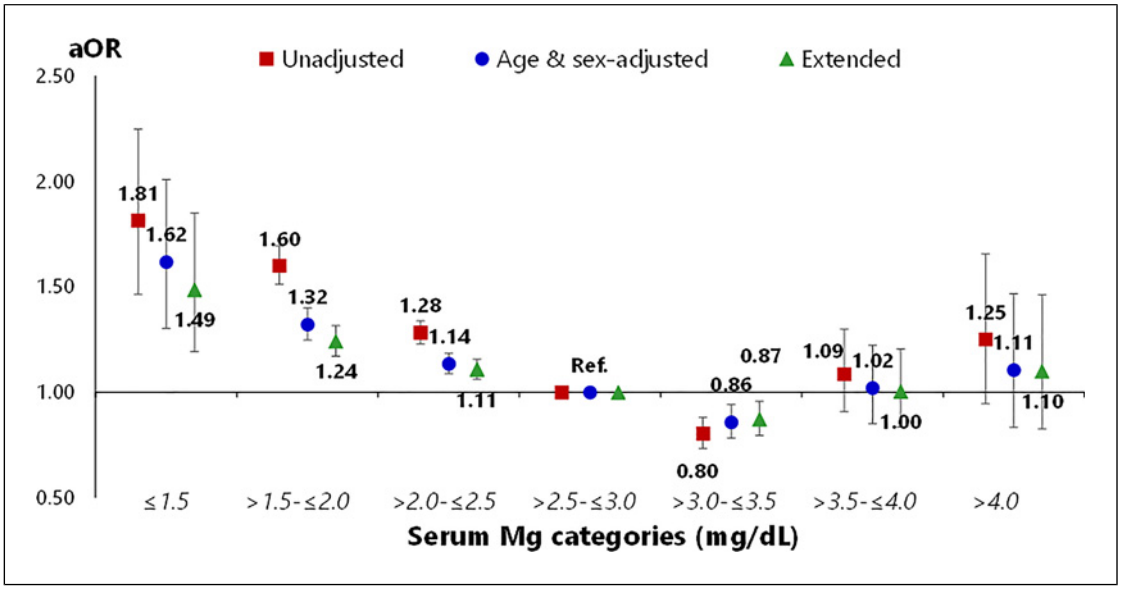

Fig. 2. Associations between sMg and prevalent AF (n = 165,926). Odds ratios (ORs) were estimated with logistic regression models. Red squares indicate ORs from the unadjusted model. Blue circles indicate ORs from the age- and sex-adjusted model. Green triangles indicate ORs from the extended model adjusted for age, sex, body mass index, smoking, diabetes, IHD, ultrafiltration volume, and dialysis time. Error bars indicate 95% CIs (n = 165,926). aOR, adjusted odds ratios; Mg, magnesium.

Table 2. Associations of AF with sMg and covariates (n = 165,926)

	Adjusted OR, point estimate (95% CI)	p value
sMg		
≤1.5 mg/dL	**1.49 (1.19–1.85)**	<**0.001**
>1.5–≤2.0 mg/dL	**1.24 (1.17–1.32)**	<**0.001**
>2.0–≤2.5 mg/dL	**1.11 (1.06–1.16)**	<**0.001**
>2.5–≤3.0 mg/dL	Reference	
>3.0–≤3.5 mg/dL	**0.87 (0.79–0.96)**	0.004
>3.5–≤4.0 mg/dL	1.00 (0.84–1.20)	0.971
>4.0 mg/dL	1.10 (0.83–1.46)	0.516
Age, per 10-year increase	**1.52 (1.50–1.55)**	<**0.001**
Men	**1.29 (1.24–1.34)**	<**0.001**
Diabetes	0.99 (0.95–1.03)	0.666
Current smoker	1.04 (0.97–1.11)	0.243
BMI, per 1-kg/m^2 increase	1.00 (0.99–1.01)	0.875
IHD	**1.48 (1.42–1.54)**	<**0.001**
SBP, per 10-mm Hg decrease	**1.17 (1.16–1.18)**	<**0.001**
Ultrafiltration volume, per 1-kg increase	**1.12 (1.09–1.14)**	<**0.001**
Treatment time, per 1-h increase	**1.10 (1.07–1.14)**	<**0.001**

Odds ratios for the presence of AF were estimated in a logistic regression model with all covariates listed in the table. Bold values indicates a statistically significant relationship. OR, odds ratio; CI, confidence interval; BMI, body mass index; IHD, ischemic heart disease; SBP, systolic blood pressure.

Table 3. Population-attributable fraction for AF† (n = 165,926)

	Estimates (95% CI)
Serum magnesium	
Scenario 1 (if all categories are replaced by >2.5–≤3.0 mg/dL)	6.9% (4.3–9.3)
Scenario 2 (if all categories below ≤2.5 mg/dL are replaced by >2.5–≤3.0 mg/dL)	7.4% (5.1–9.7)
IHD	
Scenario (if all patients are free of IHD)	10.8% (9.7–12)

†Estimated from a logistic model with magnesium, age, sex, diabetes, current smokers, BMI, IHD, systolic blood pressure, ultrafiltration volume, and treatment time as explanatory variables. Although not potentially amenable to intervention, a scenario without IHD was estimated for comparison of the magnitude of the fractions. CI, confidence interval; BMI, body mass index; IHD, ischemic heart disease.

hemodialysis patients with secondary hyperparathyroidism reported an increased prevalence of AF among those with sMg <2.3 mg/dL. However, this study did not investigate further differences in the prevalence of AF within that sMg category [5]. Although arrhythmias in hemodialysis patients detected by continuous electrocardiographic monitoring with loop recorder implantation are reported to occur less frequently with higher sMg, AF accounted for only 35.4% (4,419 out of 12,480 events) of the arrhythmias detected; therefore, the genuine association between sMg and AF incidence is still not clear [14].

Hypomagnesemia affects the conduction system of the heart and can cause arrhythmias of atrial and ventricular origin. Both extracellular and cytoplasmic magnesium can affect cardiac ion channels and consequently influence action potential duration, cell excitability, and contractility [15]. Hypomagnesemia may also contribute to AF via inflammation and endothelial dysfunction [16]. Indeed, magnesium depletion caused by a magnesium-restricted diet was reported to induce AF, and magnesium replenishment abolished AF [17]. This study has several clinical implications. First, this study raises the need to discuss optimal sMg values to reduce the AF burden. Based on our study as well as previous studies [5, 18], we suggest that optimal sMg in hemodialysis patients should be 2.5–3.0 mg/dL. The sMg category associated with the best survival rates reported in a Japanese nationwide cohort study was 2.7–3.0 mg/dL [18], which is covered by the sMg reference category in this study. This sMg range is above the general population's reference values. However, since the ratio of ionized magnesium to sMg values was shown to be decreased in hemodialysis patients [19], it remains unclear whether ionized magnesium concentrations are higher in hemodialysis patients than in the general population within this sMg range. Therefore, maintaining sMg values higher than those in the general population is reasonable for hemodialysis patients to keep the biologically active form of magnesium within the normal range. Further, there was a nonsignificant trend toward a higher prevalence of AF at sMg levels >4.0 mg/dL. Although the underlying reason is unclear, sMg levels >4.0 mg/dL have been generally associated with an increased risk of bradyarrhythmia [20]. However, it is important to consider a safety upper bound for sMg levels. In addition, it is important to consider the upper limit described in previous studies, which found that a sMg level >3.0 mg/dL is associated with all-cause and cardiovascular mortality [18]. Second, the population-attributable fraction value of sMg for AF in this study was similar to that of IHD and therefore, the magnitude of that value should be considered non-negligible. It was greater than the population-attributable fraction value of the history of cardiac disease for AF shown in the ARIC study involving the general population [21]. Taken together, health policymakers and dialysis providers should consider uncontrolled sMg levels as potentially important contributors to AF in hemodialysis patients, rather than merely an adjunct mineral abnormality [5]. The impact of uncontrolled sMg estimated at the population level has been reported even with death as an outcome [5]. Further investigation is warranted for incorporating assessment and management of sMg levels into future guidelines for mineral abnormalities in hemodialysis patients. Third, sMg values should be checked when AF is detected in clinical practice. Even if sMg is within the reference range for the general population, we need to consider that it may be suboptimal for dialysis patients. Conversely, pulse palpation and ECG should be checked for the presence of AF if hypomagnesemia is found in a dialysis patient. Fourth, sMg is potentially modifiable. In hemodialysis patients, dialyzate magnesium concentrations can be a potential target for intervention. In fact, the use of high dialysate Mg concentration (1.75 mEq/L, equivalent to 2.13 mg/dL) has been shown to increase sMg and ionized magnesium concentration compared to the standard dialysate Mg concentration (0.70 mEq/L, equivalent to 0.85 mg/dL) [22]. However, excessively

high sMg levels in dialysis patients may be associated with an increased risk of mortality [18]. Therefore, trials targeting optimal sMg ranges in hemodialysis patients are needed.

This study has several strengths. First, the findings of the present study are highly generalizable because the analysis is based on nationwide data. Second, the large sample size allowed precise estimation of the correlation between sMg and the prevalence of AF and population-attributable fraction values of sMg. Third, consideration of the DAG, including hemodialysis-specific confounding such as ultrafiltration volume and dialysis time, allowed to minimize bias during the analysis of the correlation between sMg and the prevalence of AF.

This study also has few limitations. First, the possibility of reverse causation cannot be ruled out. However, it seems biologically implausible. If the patient has AF and, therefore, difficulty in continuing hemodialysis, then a decrease in sMg is unlikely to occur, considering that the dialysate magnesium concentration in Japan is 1.0 mEq/L (1.22 mg/dL equivalents) [5]. Second, as with other studies [23], data on serum potassium concentration were not available. Low sMg can be associated with low serum potassium in hemodialysis patients [5]. However, a previous study showed that the correlation between sMg and AF remained unchanged with or without adjusting for serum potassium [4]. In addition, the aforementioned study of arrhythmias detected by continuous monitoring with loop recorder also failed to show any association of serum potassium with their incidence [14]. Further, by evaluating DAG including serum potassium, we were able to analyze the correlation of sMg with AF using a minimal sufficient adjustment set without including serum potassium. Thus, it seems unlikely that serum potassium levels explain the observed association. In addition, data regarding potassium binders were unavailable. Therefore, we could not examine their impact on the relationship between sMg and AF. However, a previous clinical trial indicated that there was insufficient evidence regarding the use of potassium binders being a significant causative factor for hypomagnesemia [24]. Third, we were unable to identify the AF subtype (paroxysmal, persistent, or chronic). The association of AF with dialysis time and ultrafiltration volume shown in this study evokes the paroxysmal AF triggered by dialysis. Meanwhile, a single measurement of the 12-lead ECG at any given time may miss the detection of paroxysmal AF. The lower prevalence of AF among hemodialysis patients in this study compared with that in the USA [2] and other countries may be attributed to the single measurement. However, the multinational Dialysis Outcomes and Practice Patterns Study reported that the prevalence of AF in Japan was significantly lower (0.67 times) than that in the USA; moreover, the prevalence of AF in Japan in this previous study (5.6%) was similar to that in our study [25].

Based on the analysis of Japanese nationwide data, the prevalence of AF is increased in hemodialysis patients even when sMg is in the reference range for the general population, and the prevalence is higher with lower sMg. The population-attributable fraction for AF due to uncontrolled sMg was non-negligible. Longitudinal studies are needed to identify the optimal range of sMg to reduce AF minimally.

Acknowledgments

The results reported in this study have been achieved using the data from Japanese Society for Dialysis Therapy (JSDT) Renal Data Registry. The interpretation and reporting of these data are the responsibility of the authors and in no way should be seen as an official policy or interpretation of the JSDT.

Statement of Ethics

The present study was conducted following Japan's privacy protection laws and ethical guidelines for epidemiological studies published by the Ministry of Education, Science and Culture, the Ministry of Health, Labour, and Welfare, and the STROBE guidelines. The study protocol was approved by the Medicine Ethics Committee of the JSDT (No. 56). The data used in this study contained no identifying personal information. The requirement for informed consent was waived by the Medicine Ethics Committee of the JSDT.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Tatsunori Toida and Noriaki Kurita designed the study, analyzed the data, and wrote the initial draft of the manuscript. Nobuhiko Joki contributed to the analysis of the data and managed the dataset.

Supervision was done by Masanori Abe and Norio Hanafusa. Noriaki Kurita, Masanori Abe, Norio Hanafusa, and Nobuhiko Joki contributed to the design of the study and data interpretation.

Data Availability Statement

Data are available with the permission of the JSDT.

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