



## RESEARCH PAPER

# Epidemiology of ALS in Korea using nationwide big data

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## ABSTRACT

**Objective** This study aimed to determine the incidence, prevalence and survival time of Korean patients with amyotrophic lateral sclerosis (ALS) using National Health Insurance Service (NHIS) data.

**Methods** Using NHIS data, the Korean nationwide health dataset, we identified patients with motor neuron diseases who were first diagnosed with a KCD-6 code (G12.20–G12.28; modified from ICD-10 codes) between 2011 and 2015. ALS (G12.21 code) epidemiological characteristics, including annual incidence, prevalence, mortality rates and survival time, were analysed and compared with sociodemographic variables.

**Results** New patients with ALS (n=3049) were enrolled over 5 years. The mean annual incidence was 1.20/100 000, and the sex ratio was 1.60 (male:female). The mean age at the time of diagnosis was 61.4 years. The prevalence rate was 3.43/100 000 in 2015. In this period, riluzole was prescribed to 53.6% of patients with ALS. Furthermore, 20.3% of patients with ALS underwent tracheostomy. When analysed for age and socioeconomic status, ALS prevalence rate was 10.71 in the aged group (≥60) in 2015 and was lowest in the middle-income group compared with that in the high-income and low-income groups. The estimated mean survival time in this population was 50.0 months, and the 3-year and 5-year mortality rates were 52.1% and 63.7%, respectively.

**Conclusions** This study is the first nationwide survey for epidemiological characteristics of ALS in Korea using national data. The use of these data substantially advances the understanding of Korean and Asian ALS epidemiology and its relationship with socioeconomic status, age and sex.

## INTRODUCTION

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease characterised by the progressive degeneration of motor neurons, which leads to impairment of limb and bulbar function and ultimately death due to respiratory failure.<sup>1,2</sup> Despite considerable recent advances in clinical and basic research on ALS, its clinical heterogeneity remains poorly understood.<sup>3</sup> Recent studies on ethnic differences in ALS's causative genes, the role of environmental factors in its aetiology and a conceptual paradigm shift from understanding ALS as a classic motor neuron disease to a motor network syndrome may collectively provide some clues for better understanding the racial differences underlying ALS's unique epidemiology and prognosis.<sup>4,5</sup>

The incidence of ALS in European studies was reported as 2–3 per 100 000,<sup>6–8</sup> 0.3–0.6 in Taiwan and China<sup>9–11</sup> and 1.68 person-years of follow-up (PYFU) worldwide.<sup>12</sup> The survival time from disease onset is also considerably variable by population<sup>13</sup>; it was reported to be 30 months in European samples,<sup>6</sup> 71 months in China<sup>1</sup> and 48 months in Japan.<sup>14</sup> The epidemiological characteristics of patients with ALS are variable by patient nationality, region and race. In addition, studies on the epidemiological characteristics of ALS have been conducted mostly in Europe and North America, whereas those in Asia have been limited.<sup>7</sup> It should be noted that even within Asian countries, epidemiological data are dissimilar,<sup>15</sup> and Korean data have been limited to one cross-sectional study.<sup>16</sup> We assumed that these differences in epidemiological data in ALS were due to ethnic or genetic differences and also to heterogeneity of the denominator databases, such as a nationwide population-based study, hospital-based study or registry-based study. In this study, we conducted an epidemiological study using a nationwide population-based database. The present study sought to investigate the incidence, prevalence and survival of ALS based on population-based Korean National Health Insurance Database (NHID) data.

## MATERIALS AND METHODS

### National health insurance in Korea

National Health Insurance System (NHIS) coverage in Korea is provided by a single insurer (the central government) for the entire population and as such follows a social health insurance scheme. As of 2016, 97.1% of the population was covered by health insurance, and 2.9% were covered by medical aid.<sup>17</sup>

NHIS in Korea provides data through the National Health Insurance Database (NHID) for research purposes only. These data include information on the insured population's sociodemographic characteristics, income-based insurance contributions, medical treatment records, long-term care insurance information for elderly patients, the status of medical institutions, and rates of cancer and rare incurable diseases.

In Korea, all medical institutions nationwide are contracted by the national government under a mandatory system and operate based on a regulated fee-for-service system. All prescriptions, orders and diagnostic codes are computerised and gathered in the NHID. Given this, the NHID provides data that



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more accurately represent the entire population than an individual, smaller sample could. Therefore, we used the NHID here to derive the most accurate epidemiological data for the entire Korean population.

### Korean Classification of Disease (KCD) code for motor neuron diseases and diagnosis rates

Statistics Korea has developed the Korean Classification of Disease (KCD 5–7) based on International Classification of Disease and Related Health Problems 10th Revision (ICD-10). Until 2010, all patients with ALS or other types of motor neuron diseases (MNDs) were designated with a G12.2 code, which aligns with a KCD-5 code. Therefore, it was impossible to identify sporadic or familial forms of ALS from a spectrum of MNDs in the NHID until 2010. In 2011, however, more detailed codes (G12.20–G12.28 or KCD-6) were adopted to differentiate between specific types of MNDs. For example, familial and sporadic ALS were coded as G12.20 and G12.21, respectively, and G12.22 (primary lateral sclerosis), G12.23 (progressive bulbar palsy), G12.24 (progressive muscular atrophy) and G12.28 (other and unspecified motor neuron disease) were further subclassified within the broader KCD-6 category.

In the present study, novel G12.21 (KCD-6) codes identified at least once in the NHID between January 2011 and December 2015 were used to define newly registered, sporadic patients with ALS. Although these patients were not classified based on the El Escorial Criteria—Revised categories (clinically definite, clinically probable, clinically probable with laboratory supportive, or clinically possible), they were compatible with one of them.<sup>18</sup>

The total number of patients diagnosed with a G12.20–G12.28 code was 7672 between 2011 and 2015, and the number of sporadic patients with ALS with a G12.21 code was 3049 in the same period. These constituted our final study subjects for survival analysis.

### Incidence, prevalence and survival time of Korean patients with ALS

From 2011 to 2015, newly registered patients with ALS and the standard population (denominator) in each year were identified using a NHID subdatabase (DB)—the healthcare use DB and the eligibility DB. During the study period, the population of Korea (denominator) was ageing. In 2011, the population over the age of 60 was 15.3%, which increased to 17.6% in 2015. Compared with the WHO standard population (2000–2025),<sup>19</sup> which is 11.95% over 60, Korea has a large population of elderly people. The male:female ratio was almost 1.00 in all years. The crude incidence and prevalence per 100 000 inhabitants were calculated using the standard population. Additionally, we calculated age-adjusted incidence and prevalence using the world standard population (WHO 2000–2025).<sup>19</sup> Furthermore, the prevalence of each MND code (G12.20–G12.28) identified in the NHID and based on a KCD-6 code was also analysed for the purpose of detecting sporadic ALS from the other MNDs. In cases where the MND diagnosis ascribed to a particular patient changed within a year, it was defined as the last diagnosis assigned that year.

In this study, we analysed the relationship between ALS and socioeconomic status, incidence and prevalence rate. ‘Income’ was categorised by income-based insurance contribution level. The ‘highest income group’ paid the highest insurance contributions and was consequently expected to have attained the highest socioeconomic level. ‘Region’ was categorised by ‘Seoul city’, which is the capital of South Korea, other ‘metropolitan city’, or

those cities excluding Seoul, and ‘other areas’, which included small and medium cities as well as rural areas.

In addition, we analysed the percentage of patients who had taken riluzole at least once and number of patients who underwent a tracheostomy during the follow-up period. Sociodemographic variables were divided according to status at the time point of first diagnosis, and the use of riluzole and/or undergoing a tracheostomy were counted at the time of event occurred during the follow-up period. Tracheostomy operations were identified by insurance payment code O1300 (invasive tracheostomy) and/or O1301 (percutaneous dilatational tracheostomy) and appropriate subcodes.

### Mean survival time of Korean patients with ALS

The survival rate and the survival time from first diagnosis of patients with ALS were analysed using Kaplan-Meier survival curves. The starting point for these analyses was defined as the date of first diagnosis. The ending point was defined as either the date of death or as 30 April 2017 for those who continued to live at study termination.

For the 3049 patients diagnosed with ALS between 2011 and 2015, patient follow-up duration ranged from a minimum of 1.33 years to a maximum of 6.33 years after first diagnosis. Previously published survival times for patients with ALS are 3–6 years.<sup>16 14</sup> Some subjects’ data were not sufficient to analyse survival time. Therefore, survival rates and survival time from first diagnosis were analysed in two different groups. That is, these analyses were independently performed on all patients (N=3049) and also in a subgroup that only included patients whose follow-up time was longer than 5 years after first diagnosis (N=714). Sociodemographic characteristics, mortality rates and mean survival time were also compared between these two groups. We analysed survival curves affected by factors including the age of diagnosis, residence and socioeconomic status using the Kaplan-Meier survival curves.

### Diagnostic delay

Using the NHID offers the significant benefit that the time of first diagnosis is likely to be highly accurate. This is because ALS is classified as a rare intractable disease (RID) in Korea, meaning that patients with ALS are financially supported by the government RID registry programme and have co-payment reduction benefits.

Accurately determining the duration from the time of symptom onset to ALS diagnosis (diagnostic delay) was challenging. Diagnostic delay was the mean time duration between symptom onset to the time of first diagnosis. We estimated this mean diagnostic delay time from data provided by the ALS clinic in the department of neurology at Hanyang University Hospitals in Seoul, Korea. Diagnostic delay was estimated from 299 patients with ALS between March 2009 and June 2017. All patients fulfilled the revised El Escorial criteria. The mean diagnostic delay was 11.7 months (median, 9 months). Given this, we performed true survival time estimates by adding 11.7 months to survival time after first diagnosis.

### Statistical analyses

We calculated the estimated incidence and prevalence of ALS per 100 000 inhabitants using the eligibility DB’s annual total population as the standard population. We also calculated 95% CIs. Variables including age at first diagnosis, sex, income level and region of residence were analysed to determine whether any affected ALS incidence or prevalence rates and/or survival time.

**Table 1** Total number of newly enrolled patients with amyotrophic lateral sclerosis (ALS) and incidence rates per 100 000 inhabitants in Korea (2011–2015)

Parameters at first diagnosis	Total number (%) of new patients with ALS*	Use of riluzole %	Tracheostomy %	Incidence (per 10 <sup>5</sup> )†	95% CI
<b>Age</b>					
<40	140 (4.6)	35.7	10.7	0.11	0.07 to 0.15
40–49	335 (11.0)	60.9	16.4	0.76	0.58 to 0.94
50–59	782 (25.6)	58.2	20.6	2.04	1.72 to 2.35
≥60	1792 (58.8)	51.6	21.7	4.29	3.85 to 4.74
<b>Sex</b>					
Male	1878 (61.6)	51.8	21.5	1.47	1.32 to 1.62
Female	1171 (38.4)	56.4	18.4	0.92	0.80 to 1.04
<b>Income‡</b>					
High	1088 (35.7)	53.3	22.3	1.30	1.13 to 1.48
Middle	1174 (38.5)	56.0	20.4	1.01	0.88 to 1.14
Low	787 (25.8)	50.3	17.3	1.41	1.19 to 1.63
<b>Region</b>					
Seoul city§	601 (19.7)	55.9	21.8	1.19	0.97 to 1.40
Metropolitan¶	707 (23.2)	54.5	21.8	1.09	0.91 to 1.27
Other areas**	1741 (57.1)	52.4	19.2	1.25	1.11 to 1.38
Total	3049 (100.0)	53.6	20.3	1.20	1.10 to 1.29
adjusted incidence††				0.88	0.81 to 0.95
Age at diagnosis (mean±SD)	61.4±12.4				
Male:female ratio	1.60				

\*5 years (2011–2015) total number of new patients.

†Crude incidence rate per 100 000 inhabitants.

‡Income-based insurance contributions.

§Seoul metropolitan city.

¶Other metropolitan cities.

\*\*Non-metropolitan area.

††Age-adjusted incidence (per 100 000 inhabitants) using WHO (2000–2025) world standard population.

Mean survival time and survival rate were calculated using the Kaplan-Meier method. A log-rank test was used to analyse the difference of survival time between sociodemographic variables. In addition, 3-year and 5-year mortality rates were also analysed. All data analyses were performed using the SAS Enterprise Guide software (V.7.1; SAS Institute, Cary, North Carolina, USA).

### Data availability policy

Anonymised data will be shared by request from any qualified investigator.

## RESULTS

### Incidence and prevalence of ALS in Korea

The total number of new patients with ALS analysed across the 5 years was 3049, with an annual crude incidence per 100 000 inhabitants of 1.20 and an age-adjusted incidence of 0.88. The mean age at the time of diagnosis was 61.4 years, and the male:female ratio was 1.60 (table 1). The proportion of first-diagnosed patients with ALS were highest at the age of 60–69 years and started to decline at age 70 years (online supplementary figure e-1). The crude prevalence rate in 2015 was 3.43, and age-adjusted prevalence rate was somewhat lower than the crude rate (2.38) (table 2).

In 2015, 1770 patients with ALS visited the hospital at least once, and of these, 973 (55%) were 60 years or older. The demographic distribution of ALS prevalence did not significantly differ by year. However, prevalence was slightly lower in the middle-income group than in the high-income and low-income groups (table 2), similar to the incidence rate described in table 1.

Riluzole, the only medication approved by the FDA for the treatment of ALS at the time, was prescribed to 53.6% of all patients. The rate of patients undergoing a tracheostomy during the follow-up period was 20.3% and did not differ by age, sex, income level or region except for a decreased rate of riluzole prescription in individuals who experienced ALS onset at a young age (<40 years) (table 1).

### Proportion of patients with ALS in MND spectrum (G12.20–G12.28) in NHID

To compare the proportion of sporadic ALS (G12.21) with that of other MNDs (G12.20–G12.28), we analysed the number and proportion of each MND in the NHID.

After adopting the KCD-6 code system in 2011, the percentage of sporadic ALS (G12.21) diagnosed individuals across all MND cases (G12.20–G12.28) was approximately 50%. Of those with MND, familial ALS (G12.20, KCD-6) represented about 2.0% of the full MND spectrum, findings which mirror assumed rates based on previous genetic data.<sup>20</sup> Across the MND spectrum, the combined proportion of G12.22 (primary lateral sclerosis), G12.23 (progressive bulbar palsy) and G12.24 (progressive muscular atrophy) was less than 10% (table 3).

### Mortality

To validate and compare mortality across differing follow-up periods, which could have varying degrees of error, we analysed mortality by follow-up duration. By April 2017, 1635 (53.6%) of the total patients (n=3049) and 470 (65.8%) of subgroup patients (n=714) had died.

## Neurodegeneration

**Table 2** Epidemiological and socioeconomic characteristics of patients with amyotrophic lateral sclerosis and annual incidence and prevalence per 100 000 in Korea

Year	Incidence					Prevalence								
	2011	2012	2013	2014	2015	2011	2015	2011	2015					
<b>Characteristics at first diagnosis</b>	<b>N</b>	<b>Inc*</b>	<b>N</b>	<b>Inc*</b>	<b>N</b>	<b>Inc*</b>	<b>N</b>	<b>Inc*</b>	<b>N</b>	<b>Inc*</b>	<b>N</b>	<b>Pre†</b>	<b>N</b>	<b>Pre†</b>
<b>Age</b>														
<40	38	0.14	27	0.10	23	0.09	22	0.09	30	0.12	75	0.28	63	0.25
40–49	64	0.73	73	0.83	62	0.70	73	0.82	63	0.71	195	2.22	225	2.52
50–59	139	1.99	157	2.10	147	1.90	162	2.03	177	2.16	382	5.46	509	6.20
≥60	264	3.43	392	4.93	342	4.10	385	4.44	409	4.50	685	8.89	973	10.71
<b>Sex</b>														
Male	315	1.25	383	1.51	336	1.32	411	1.60	433	1.68	807	3.19	1072	4.15
Female	190	0.75	266	1.05	238	0.93	231	0.90	246	0.95	530	2.11	698	2.71
<b>Income‡</b>														
High	178	1.09	235	1.42	184	1.10	247	1.47	244	1.44	468	2.85	611	3.61
Middle	195	0.85	246	1.07	221	0.95	247	1.06	265	1.14	494	2.15	624	2.68
Low	132	1.19	168	1.51	169	1.53	148	1.33	170	1.50	375	3.38	535	4.72
<b>Region</b>														
Seoul city§	95	0.93	130	1.29	108	1.06	127	1.25	141	1.39	301	2.94	408	4.03
Metropolitan¶	124	0.96	130	1.03	144	1.11	153	1.17	156	1.19	331	2.57	402	3.07
Other areas**	286	1.05	389	1.38	322	1.16	362	1.29	382	1.35	705	2.58	960	3.38
<b>Total</b>	<b>505</b>	<b>1.00††</b>	<b>649</b>	<b>1.28††</b>	<b>574</b>	<b>1.13††</b>	<b>642</b>	<b>1.25††</b>	<b>679</b>	<b>1.32††</b>	<b>1337</b>	<b>2.65††</b>	<b>1770</b>	<b>3.43††</b>
Adjusted incidence/prevalence		0.79‡‡		0.97‡‡		0.83‡‡		0.89‡‡		0.92‡‡		2.07‡‡		2.38‡‡

\*Incidence rate per 100 000 inhabitants in Korea.

†Prevalence rate per 100 000 inhabitants in Korea.

‡Income-based insurance contributions.

§Seoul metropolitan city.

¶Other metropolitan cities.

\*\*Non-metropolitan area.

††Crude rate.

‡‡Age-adjusted incidence/prevalence (per 100 000 inhabitants) using WHO (2000–2025) world standard population.

The mortality was higher among the older age of onset group compared with the younger age of onset group. In the subgroup (the long-term follow-up group), the mortality of female patients was higher than that of male patients, and the middle-income group had the highest mortality. Analysis by region revealed a lower mortality among Seoul city residents than that of metropolitan cities or other areas, regardless of sampling method. Finally, the 3-year ALS mortality in this sample was 52.1%, and the 5-year mortality was 63.7 (table 4).

In many epidemiological studies of ALS, tracheostomy has been considered as death. Therefore, we performed an additional analysis with a new end-point treating tracheostomy as death; we called this the functional end-point. The functional end-point rate was 60.5% of the total patients (n=3049) and

72.8% of the subgroup patients (n=714). These results were 6.9% and 7.0% higher, respectively, than when tracheostomy is not considered as death (table 4).

### Survival time from first diagnosis and symptom onset

As with mortality, survival time was also analysed among total subjects and in the subgroup. Corrected survival time was calculated by adding the mean diagnostic delay (11.7 months) to the survival time after the first diagnosis, as explained in the Materials and methods section.

The mean survival time from first diagnosis was not significantly different between the two groups (38.3 months in the

**Table 3** Proportion of amyotrophic lateral sclerosis in the motor neuron disease spectrum (G12.20–G12.28) from 2011 to 2015

KCD-6 code*	Classification of motor neuron diseases	2011 N (%)	2012 N (%)	2013 N (%)	2014 N (%)	2015 N (%)
G12.20	Familial motor neuron disease	67 (2.4)	61 (2.2)	72 (2.4)	67 (2.0)	66 (1.9)
G12.21	Amyotrophic lateral sclerosis	1337 (48.2)	1462 (52.6)	1521 (50.4)	1676 (50.1)	1770 (50.0)
G12.22	Primary lateral sclerosis	46 (1.7)	67 (2.4)	68 (2.3)	69 (2.1)	92 (2.6)
G12.23	Progressive bulbar palsy	112 (4.0)	122 (4.4)	136 (4.5)	186 (5.6)	185 (5.2)
G12.24	Progressive spinal muscular atrophy	68 (2.5)	59 (2.1)	47 (1.6)	55 (1.6)	57 (1.6)
G12.28	Other and unspecified motor neuron disease	1145 (41.3)	1011 (36.3)	1173 (38.9)	1293 (38.6)	1373 (38.8)
	<b>Total</b>	<b>2775 (100.0)</b>	<b>2782 (100.0)</b>	<b>3017 (100.0)</b>	<b>3346 (100.0)</b>	<b>3543 (100.0)</b>

\*The KCD-6 is modified from the ICD-10.

KCD, Korean Classification of Disease.

**Table 4** Mortality (only death) and functional end-point (tracheostomy or death) of patients with amyotrophic lateral sclerosis

	Total (N=3049)*				Subgroup (N=714)†			
	Death		Tracheostomy or death		Death		Tracheostomy or death	
	N	%	N	%	N	%	N	%
<b>Age</b>								
<40	19	13.6	30	21.4	9	18.8	13	27.1
40–49	98	29.3	122	36.4	39	43.3	48	53.3
50–59	361	46.2	429	54.9	125	65.8	142	74.7
≥60	1157	64.6	1264	70.5	297	76.9	317	82.1
<b>Sex</b>								
Male	1003	53.4	1139	60.6	290	64.4	320	71.1
Female	632	54.0	706	60.3	180	68.2	200	75.8
<b>Income‡</b>								
High	590	54.2	677	62.2	160	63.5	184	73.0
Middle	629	53.6	711	60.6	190	68.1	207	74.2
Low	416	52.9	457	58.1	120	65.6	129	70.5
<b>Region</b>								
Seoul city§	303	50.4	352	58.6	81	60.4	101	75.4
Metropolitan city¶	379	53.6	436	61.7	118	67.8	130	74.7
Other areas**	953	54.7	1057	60.7	271	66.7	289	71.2
Total	1635	53.6	1845	60.5	470	65.8	520	72.8
3-year mortality (N=1946)††	1014	52.1	1202	61.8				
5-year mortality (N=714)††	455	63.7	509	71.3				

\*Total study subjects (N=3049).

†Follow-up more than 5 years from first diagnosis among study subjects (N=714).

‡Income-based insurance contributions.

§Seoul metropolitan city.

¶Other metropolitan cities.

\*\*Non-metropolitan area.

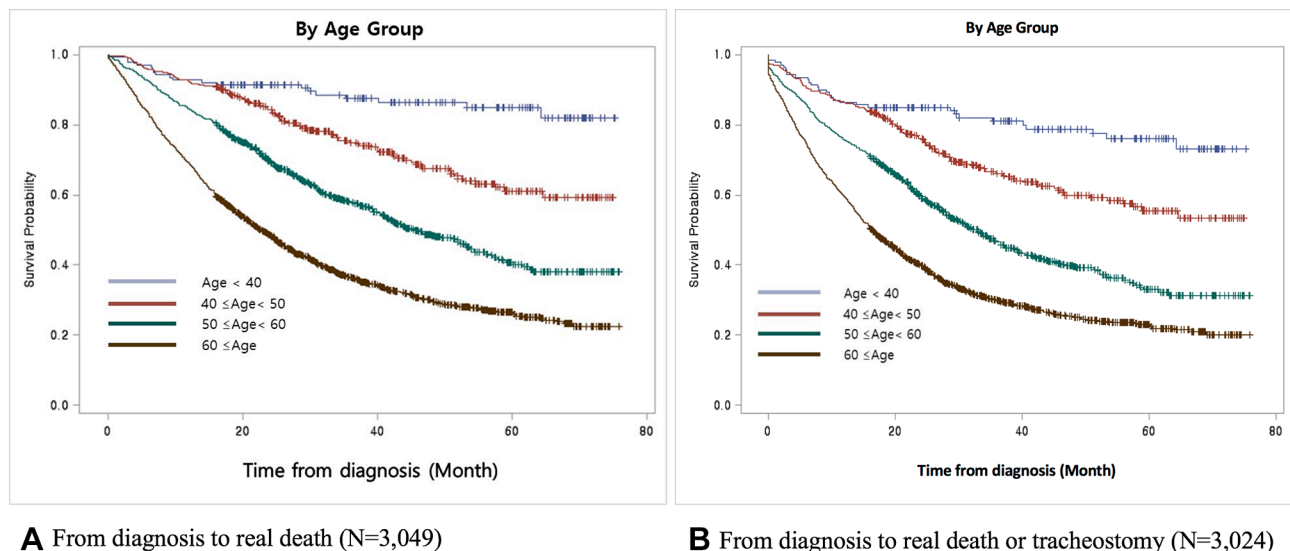
††From first diagnosis.

total subject population (n=3049) and 38.0 months in the subgroup (long-term follow-up group)).

When comparing the survival time between groups according to demographic and socioeconomic status factors, we detected only a significant difference in the mean survival time by age of onset (figure 1). Among all subjects, the survival time in the young age onset group (<40 years) was 57.7 months, while that

among the old age onset group (≥60 years) was 31.4 months (table 5).

When comparing actual death and the functional end-point (tracheostomy or death), functional end-point has a shorter survival time than actual death in the total subjects (n=3049). The survival time of functional end-point was 33.5 months from first diagnosis, which is 4.8 months shorter than that of actual



**Figure 1** Comparison of the survival curves from the time of diagnosis to the time of death in patients with amyotrophic lateral sclerosis shows significant differences in symptom onset age (2011–2015). This shows that the younger symptom onset age group had relatively longer survival time compared with that of the older group (log-rank test,  $p < 0.0001$ , both).

**Table 5** Mean survival time from first diagnosis to death (or to the end of follow-up time) or to tracheostomy or death (or to the end of follow-up time)

	Total (N=3049)*						Subgroup (N=714)†					
	Death			Tracheostomy or death‡			Death			Tracheostomy or death		
	Mean§	SE	P values¶	Mean§	SE	P values¶	Mean§	SE	P values¶	Mean§	SE	P values¶
<b>Age</b>												
<40	57.7	1.52	<0.0001	53.4	1.87	<0.0001	57.4	2.57	<0.0001	65.4	3.06	<0.0001
40–49	50.8	1.19		46.4	1.36		50.0	2.14		54.5	2.52	
50–59	40.9	0.86		35.3	0.91		37.9	1.69		40.9	1.95	
≥60	31.4	0.64		27.0	0.64		30.8	1.29		31.5	1.35	
<b>Sex</b>												
Male	36.9	0.60	0.9446	31.9	0.62	0.6788	37.0	1.17	0.4278	39.7	1.33	0.4384
Female	38.3	0.82		33.7	0.84		37.4	1.62		38.5	1.72	
<b>Income**</b>												
High	36.1	0.79	0.6515	31.0	0.81	0.1211	37.4	1.55	0.4472	40.4	1.77	0.5236
Middle	37.5	0.77		32.6	0.80		35.6	1.52		37.6	1.68	
Low	39.0	1.00		35.2	1.04		38.8	1.94		40.0	2.06	
<b>Region</b>												
Seoul city††	38.8	1.05	0.0915	32.9	1.09	0.6661	41.7	1.99	0.0887	44.2	2.23	0.5823
Metropolitan city‡‡	37.8	1.03		30.1	0.92		34.8	2.01		36.4	2.17	
Other areas§§	37.6	0.67		33.5	0.69		37.4	1.31		38.6	1.39	
Total	38.3	0.51		33.5	0.52		38.0	0.99		39.2	1.05	

All lengths of time are in months.

\*Total study subjects (N=3049).

†Follow-up more than 5 years from first diagnosis among study subjects (N=714).

‡In total study subjects, there were 25 patients who had an invalid tracheostomy date (underwent tracheostomy before amyotrophic lateral sclerosis diagnosis). When calculating functional end-point survival time in total patients group, we excluded those 25 patients (N=3024).

§Mean survival time from first diagnosis to death or to functional end-point (or to the end of follow-up time).

¶P value by log-rank test.

\*\*Income-based insurance contributions.

††Seoul metropolitan city.

‡‡Other metropolitan cities.

§§Non-metropolitan area.

death. However, in the subgroup (long-term follow-up group) analysis, survival time of functional end-point was somewhat longer (39.2 months) than that of real death (38.0 months) (table 5).

The mean diagnostic delay was analysed for all 299 patients with ALS treated at Hanyang University Hospital and was found to be 11.66±8.91 months. This diagnostic delay was adopted to calculate corrected survival time, which was 50 months among the total subjects and 49.7 months in the subgroup from initial symptom onset. The mean duration from time of first diagnosis to tracheostomy was 9.5 months.

## DISCUSSION

This study is the first to report the incidence, prevalence, survival rate and survival time of Korean patients with ALS using a nationwide population-based database, the NHID, which includes the entire Korean population. The subject of this study reflects the characteristics and latest trends in almost all occurrences of ALS in Korea as we analysed sociodemographic data only according to the specific G12.21 KCD-6 code (sporadic ALS).

The ALS incidence of 1.20 per 100 000 estimated in the present study was lower than those reported in Europe (2.08), North America (1.80),<sup>8</sup> Japan (2.2),<sup>21</sup> Italy (3.03)<sup>22</sup> and South Germany (2.5)<sup>23</sup> and higher than those reported in Taiwan (0.51), China (0.3–0.6) and Iran (0.73 PYFU).<sup>9–12</sup> When comparing European data, the incidence of Korean sporadic ALS was somewhat lower. However, when other MNDs were considered (table 3), the incidence of Korean MND was similar to that previously

reported in Ireland (1.89 per 100 000),<sup>24</sup> England (1.97, 1.35 per 100 000),<sup>25</sup> the Netherlands (2.77 per 100 000)<sup>26</sup> and France (3.32, 2.72 per 100 000)<sup>27</sup> (table 6). Because the subject criteria used for incidence calculations differ across these studies, we compared the results from several national studies and further explored the diagnostic criteria used for each (table 6).

Variations in ALS and MND incidence across populations are thought to be due to differences such as population age, economic development status, healthcare system access and genetics, such as an absence of the *C9orf72* mutation.<sup>28</sup> The incidence reported in Asian cohort studies was relatively low compared with those reported in Western-based cohort studies. The reasons why remain unclear. However, genetic differences represented by the *C9orf72* mutation have emerged as one possible cause for population diagnosis rate disparities. In a previous genetic study conducted by our group, the most common mutation in the European ALS population, the *C9orf72* mutation, was absent in the Korean population. Moreover, known ALS genes, an aspect of genetic heterogeneity, have been detected at a relatively low rate in the Korean ALS population compared with that in the European population.<sup>29</sup> Furthermore, Korean patients with ALS may have a different genetic background from other ethnicities with a low rate of familial ALS and exhibit a distinct distribution of genetic variants. Common genes including *C9orf72*, *TARDBP* and *OPTN* have not been found in familial and sporadic Korean patients with ALS.<sup>20 30 31</sup>

Furthermore, these differences may arise owing to methodological heterogeneity. As shown in table 6, studies showing a

**Table 6** Comparison of incidence and prevalence rate of patients with amyotrophic lateral sclerosis (ALS) between various countries

Study location	Race	Data source	Study design	Diagnostic criteria (for incidence)	Year	Number of new patients with ALS	Incidence* (per 10 <sup>5</sup> )	Prevalence* (per 10 <sup>5</sup> )
HKSAR <sup>10</sup>	Chinese	CMS (clinical management system)	Hospital-based (multicentre)	MND on the revised EEC+ICD-9 code 335.2, 335.20–335.24	1997–2002	98	0.60†	3.04†
Japan <sup>21</sup>	Japanese	Nationwide mail survey	Population-based	Definite, probable or possible ALS based on the revised EEC	2009	2264	2.2	9.9
Taiwan <sup>9</sup>	Chinese	Health insurance	Population-based	Repeated claim with ICD-9 code 335.20 (amyotrophic lateral sclerosis) either outpatient or inpatient	2007	338	0.51	1.97
Ireland <sup>24,‡</sup>	Caucasian	Ireland‡ MND registers	Population-based	Definite, probable, possible and suspected MND/ALS using the original EEC	2004–2005	109	1.89§	4.99
England <sup>25</sup>	European origin/African origin	The South East England ALS (SEALS)	Population-based	Data derived from SEALS register	2002–2008	88	1.97§ ¶ ** 1.35§ ** ††	5.79¶ ¶ 4.94 ††
Netherlands <sup>26</sup>	Caucasian	Population-based registry	Population-based	Definite, probable, possible or suspected ALS according to the EEC+PMA‡‡, PLS§§, PBP¶¶	2006–2009	1217	2.77§	10.32
France <sup>27</sup>	Caucasian	Health insurance	Population-based	At least one delivery of riluzole or hospitalisation for MND (claim with ICD-10 code G122)	2012–2014	6553	3.32§ 2.72§ **	NA
Italy <sup>22</sup>	Caucasian	PARALS***	Community-based Cohort study	Definite, probable or possible laboratory-supported ALS based on the revised EEC (EEC before 2000)	1995–2014	2702	3.03 2.78**	10.54
Southern Germany <sup>23</sup>	Caucasian	The ALS registry Swabia	Community-based cohort study	Definite, probable or possible ALS based on the revised EEC (cases comprise the ICD-10 code G12.2)	2008–2010	438	2.5† §	NA
Worldwide <sup>12</sup>	All races	From 44 studies	Meta-analysis			13 146	1.75§ 1.68† §	NA
South Korea (current study)	Korean	Health insurance	Population-based	First service claim with KCD-6 code G12.21 (amyotrophic lateral sclerosis)	2011–2015	3049	1.20	3.43

MND, motor neuron disease; EEC, El Escorial criteria; NA, not applicable.

\*Crude rate.

†Age-standardised incidence rates.

‡Both Northern Ireland and the Republic of Ireland.

§Per 100 000 person-years.

¶European ancestry group live in inner city London.

\*\*The age-adjusted and sex-adjusted incidence rate.

††African ancestry group live in inner city London.

‡‡Progressive muscular atrophy.

§§Primary lateral sclerosis.

¶¶Progressive bulbar palsy.

\*\*\*The Piemonte and Valle d'Aosta Register for ALS.

relatively high incidence targeted a wider range of the disease spectrum, including MND, and used hospital-based or registry-based databases. In this study, only patients with ALS (G12.21) were recruited through a nationwide population-based database, NHID. Other spectra of MND (G12.20, G12.22–G12.28) were excluded to apply strictly the KCD-6 diagnostic code system, which was based on the updated ICD-10 classification system. This may explain the low incidence of ALS found in the Korean sample studied here.

We reveal here that the Korean prevalence of ALS per 100 000 was 3.43 in 2015. These figures are lower than those reported by studies performed in Europe—which report 7.0–9.0 per 100 000<sup>6–8 32</sup>—as well as in India (4.0)<sup>15</sup> and Japan (11.3),<sup>8</sup> but are similar to American estimates (3.40).<sup>8</sup> The prevalence of ALS in China and Taiwan have been reported to be lower than what we report here in Korea.<sup>9–11</sup> An increased prevalence in some populations may be influenced by an improved detection capability via a nationalised health registration system, especially when this system tracks patients over time rather than only on their initial registration, for the KCD-6 code G12.21 or comparable codes.<sup>6</sup> A further factor that influences these estimates may be the accumulation of patients over time, as populations vary in terms of size and growth rates.<sup>9</sup> Additionally, due to an increase in the use and government support of portable, at-home ventilators and the advent of clinics that use a multidisciplinary approach, the prevalence of ALS in Korea is also expected to increase gradually.<sup>33–35</sup> Considering that the age-adjusted prevalence was lower than the crude rate and rose more slowly, the ageing population of Korea over the 5-year study period would also have affected the prevalence (table 2).

The estimated survival time for individuals with ALS in the present study was 50 months, similar to that reported in a Japanese study (48 months)<sup>14</sup> and in European studies (3–5 years).<sup>3</sup> However, this Korean survival time was notably shorter than that reported in a Chinese study (median of 71 months).<sup>1</sup> While this differed from our findings by including more severe clinical cases, the survival time of individual patients ranged from several months to over 10 years.<sup>1 13 32</sup> In addition, some proportion of patients die without ever receiving a diagnosis and many regional, socioeconomic, disease awareness, accessibility of medical institutions and cultural differences exist between national populations, further increasing variability. Therefore, it is difficult to compare the survival time simply by mean or median. An additional factor that may have contributed to the increase in survival time in the Korean population reported here include the fact that ALS is part of a RID registry programme in NHIS. This programme allocates patients with RID benefits including reduced co-payments and a government-sponsored ventilator, which may provide some with a financial incentive for seeking this diagnosis.<sup>36–38</sup>

There are many reports that the use of riluzole may increase survival time in individuals with ALS.<sup>39–41</sup> Among those with a KCD-6 code G12.21 diagnosis, the use of riluzole was 53.6% here, which is lower than the 65.3% derived from the PRO-ACT database<sup>13</sup> and higher than the 32.3% reported in a Chinese study.<sup>1</sup> In Korea, it is possible to obtain riluzole with insurance benefits if an individual's ALS diagnosis meets the El Escorial revised criteria for patients with ALS diagnosed as clinically probable or clinically definite.

A limitation of this study is that NHID is not intended or designed for research purposes, but rather for processing insurance claims, and it is thus difficult to extract completely accurate clinical progress or clinical findings data for all subjects. Furthermore, unlike hospital-based databases, individual clinical information was not included in the NHID; such information included symptom onset, onset type, progression rate, family history, result of neurological examination or laboratory tests, and history of alcohol or smoking. These data would be helpful to validate the currently available survival prediction tools such as presented by Knibb *et al.*<sup>42</sup> There is also the possibility that patients who presented with atypical phenotypes were provided a non-specific code diagnosis, such as G12.28. As demonstrated in table 3, patients with a G12.28 code diagnosis (other and unspecified MND) were included more in the present cohort than was expected based on clinical experience. Additionally, we speculate that some patients with ALS do not present with clinical characteristics which fulfil the El Escorial Criteria and could have instead have been initially registered with another code, such as G12.28. Patients with other types of MNDs, such as primary lateral sclerosis or progressive bulbar palsy, which are difficult to diagnose early, may also have been assigned the G12.28 code initially. Additionally, because of the unique medical health insurance system in Korea, patients can be managed at an oriental herbal medicine hospital or nursing hospital prior to being directed to a general hospital. These patients were excluded from the present study because the accuracy of their diagnosis, even if they were assigned a G12.21 code, could not be trusted. As a result, the incidence and prevalence of this study may be somewhat underestimated. However, this also caused our research subjects to be selected by relatively strict criteria.

Despite these limitations, however, the data reported here greatly advance current understanding of the epidemiological characteristics of ALS in Korea. As with other rare diseases, it is difficult to investigate associated epidemiological data. Bae *et al* reported on the difficulty of collecting accurate epidemiological data on degenerative neurological disease other than ALS.<sup>16</sup> Hardiman *et al* (2017) also pointed out that prospective population-based registration is a very valuable resource in assessing trends in rare diseases.<sup>6</sup> Because NHIS is mandatory for all medical service providers and patients in Korea, we were able to collect and investigate a large quantity of epidemiological information on Korean patients with ALS. NHIS covers almost the entire Korean population (97.1%), so the NHID represents real-world data,<sup>43</sup> based on actual patient claims and provider billing activities.

This study is the first to report the incidence and prevalence of ALS, as well as the survival rate and time of patients with ALS, in Korea using a population-based database including almost the entire population. Through the present study, we were able to examine the scope and sociodemographic characteristics of ALS in Korea. The incidence and prevalence of ALS categories defined by income-based insurance data revealed a bimodal distribution. Furthermore, patients living outside of the city of Seoul had a shorter survival time than those living in Seoul. Based on this, we hypothesise that urban-dwelling patients access multidisciplinary medical services more easily. Between 2011 and 2015, Korean patients with ALS were classified with a KCD-6 code, as per the ICD-10. This period was selected because the disease classification was made clearer in 2011, and its duration allowed for sufficient assessment of mortality rates. Further research is needed to analyse data collected from the 5 years subsequent to 2016, when the KCD-7 was applied. Further details, including natural historical data, are also needed for a

more comprehensive understanding of the characteristics of ALS and MNDs more broadly in Korea.

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