Suicide Attempts in Patients With Amyotrophic Lateral Sclerosis:

An Analysis of the Korean National Health Insurance Database

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Abstract

Objective: The knowledge of the common risk factors for suicide attempts may not be simply applicable to patients with amyotrophic lateral sclerosis (ALS). We aimed to identify risk factors associated with suicide attempts in patients with ALS and to determine the annual prevalence and periods of vulnerability associated with attempts.

Methods: This nationwide cohort study was performed using the Korean National Health Insurance Database. All patients with ALS concomitantly registered for the Exempted Calculation of Health Insurance for rare, incurable diseases between 2011 and 2017 were identified. We used the Cox proportional hazards regression model and competing risk model to identify the risk factors for suicide attempts. The multivariable models were adjusted for potential risk factors from the univariate analysis.

Results: Among 2,955 incident patients, 47 attempted suicide. After adjusting for sex, previous attempts, and previous psychiatric disorders, the hazard ratios for psychiatric hospitalization before ALS diagnosis were 3.17 (95% confidence interval [CI], 1.31–7.70; $P = .01$) and 3.02 (95% CI, 1.32–6.90; $P = .01$) in the Cox regression model and the competing risk model, respectively. The annual prevalence of suicide attempts was 0.29%–1.12%. Twenty (42.6%) and 9 (19.1%) attempts occurred within 3 months and 12–18 months after diagnosis, respectively.

Conclusions: Psychiatric hospitalization increased the risk of suicide attempts, which clustered at the early stage or on losing autonomy. Those with a history of psychiatric hospitalization should receive an in-depth evaluation and be cautiously monitored.

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Amyotrophic lateral sclerosis (ALS) is a devastating neurodegenerative disease characterized by the progressive degeneration of both the upper and lower motor neurons.[1] ALS is considered a spectrum disorder involving clinical, histopathological, and genetic overlap with frontotemporal dementia.[2] As a result, individuals diagnosed with ALS may have symptoms such as memory impairment, executive dysfunction, and behavioral changes.[3] Additionally, accumulating evidence suggests that patients with ALS are more likely to develop major depressive disorder than are ALS-free individuals.[4–6] Globally, suicide, which is the endpoint of the suicidal process and not an instantaneous event, is a leading cause of death[7]; the process starts with hopelessness in response to surroundings, followed by suicidal ideation, which leads to suicidal plans, suicide attempts, and, eventually, suicide. Because grave medical conditions force people to closely face issues of their death,[8] the diagnosis of an incurable disease such as ALS may elicit reactive hopelessness in some patients; this could lead to the initiation and progress of the suicidal process[9,10] and increase the risk of depression,[11] which increases the risk of suicide attempt.[10] Patients with ALS constitute a unique group, to which the knowledge of the common risk factors of suicide attempt, such as female sex, younger age, and a prior psychiatric disorder,[12] might not simply be applicable because of their group-specific aspects; the patients experience relentlessly progressive motor symptoms such as extremity weakness, dysarthria, and dysphagia, while their alert mental status is maintained, and there is currently no effective treatment that can halt or reverse the progression of disease. The prevalence of suicide attempts among patients with ALS also remains unknown. It is, therefore, of great importance to directly

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Clinical Points

- The common risk factors for suicide attempts may not be directly applicable to patients with amyotrophic lateral sclerosis (ALS) due to their group-specific characteristics.
- Patients with ALS who have a history of psychiatric hospitalization are at an increased risk of suicide attempts.
- Suicide attempts in patients with ALS tend to occur early in the disease course or after loss of autonomy.

evaluate data on patients with ALS who have attempted suicide to build efficient strategies for the identification of those at risk. However, thus far, only a limited number of studies have addressed this issue; those studies indicate that the suicide rates among individuals with ALS are 21.4 to 100 times higher than what would be expected in the general population of their respective countries.[13]

The purposes of this study were to identify the risk factors associated with, to evaluate the annual prevalence of, and to determine the period of vulnerability for suicide attempt among patients with ALS. Because ALS is a rare disease and a suicide attempt is also a rare event even in psychiatric patients, we used a large longitudinal claims dataset from the Korean National Health Insurance Service (NHIS) to obtain nationally representative data.

METHODS

This study was approved by Inha University Hospital Institutional Review Board (2020-02-027), and the need for informed consent was waived. The personal privacy of the study subjects was protected through the deidentification of the national insurance data.

Study Population

We analyzed the data on a longitudinal sample of patients diagnosed with ALS during 2011–2017, which was retrieved from the National Health Insurance Database (NHID), developed by the NHIS. All diagnostic codes, medications, and medical services are computerized and gathered in the NHID. The NHIS is provided by the Korean government, and residents of Korean nationality and foreign residents who want to join are enrolled in the NHIS either as NHI beneficiaries or medical aid recipients.[14] In Korea, all health care institutions are subject to the mandatory designation system of the NHIS, operated based on regulated fee-for-service payment.[14] As such, the NHID is a nationwide source of epidemiologic data on health care utilization. The anonymized claims data contain information on diagnoses according to the *Korean Standard Classification of Diseases* (*KCD*), which is based on the *International Statistical Classification of Diseases and Related Health Problems, 10th Revision*,[15] and on prescribed drugs and procedures according to the NHID formulary code.

Selection Criteria

We defined patients with ALS who were assigned a *KCD-6* (2011–2015) or *KCD-7* (2016–2017) code of G12.20 or G12.21 at least once and were concomitantly registered under V123 for the Exempted Calculation of Health Insurance for rare, incurable diseases. Period prevalent patients for a specific year were defined as those who were diagnosed with ALS at least once during the specified period. With the year of 2011 set as a washout period, incident patients for a specific year were defined as those who received ALS diagnosis for the first time during the year. The index date was defined as the first date of ALS diagnosis. Patients who underwent gastrostomy (M6730, Q2612, Q2613, or Q2614) and tracheostomy (O1300 or O1301) were identified through the NHID insurance payment codes.

Outcome Variable and Follow-Up

Each case in the study population was followed up from the index date until the date of index suicide attempt, which is defined as the first suicide attempt after ALS diagnosis, the date of all-cause death, or the end date of the study period (December 31, 2017), whichever came first. Suicide attempt was operationally defined with the following *KCD* codes, mainly based on a Danish register–based algorithm for the identification of suicide attempt,[16] with a minor modification by the authors: (1) X60–X84; (2) Y10–Y34 and Y87.0 with an F code ("mental, behavioral, and neurodevelopmental disorders")[15]; (3) T36–T38, T40–T41, T44–T50, T52–T57, T59–T60 with an F code and T39, T42–T43; (4) S51, S55, S59, S61, S65, or S69 with an F code; and (5) T58 (Supplementary Table 1). The cases with both and X or Y code and a code specifying a detailed method were classified as belonging to the latter. "Intentional self-harm," "intentional self-poisoning," and "intentional self-injury" were categorized as (1), (3), and (4), respectively. Annual period prevalence of suicide attempts was calculated as the number of index suicide attempts divided by the number of prevalent patients during a particular year.

Potential Risk Factors of Suicide Attempt

We included the following a priori variables in the analysis as potential risk factors: sociodemographic variables; neurologic variables such as the heritability of ALS, riluzole prescription, gastrostomy, and tracheostomy; and psychiatric variables. Income was classified as low, middle, or high if the patients were in the bottom 40% or were medical aid recipients, in the bottom 41%–80%, or in the top 20% of all households, respectively. Metropolitan cities include the 7 most

Table 1.
Characteristics of Prevalent Patients With ALS

Characteristic	2011	2012	2013	2014	2015	2016	2017
Prevalent patients, n (% male)	1,511 (59.8)	1,620 (59.1)	1,693 (57.7)	1,881 (59.4)	2,058 (60.4)	2,139 (58.5)	2,238 (58.2)
Familial ALS[a]	73 (67.1)	50 (72.0)	52 (76.9)	63 (76.2)	58 (79.3)	80 (73.8)	100 (69.0)
Sporadic ALS[b]	1,438 (59.5)	1,570 (58.7)	1,641 (57.1)	1,818 (58.8)	2,000 (59.9)	2,059 (57.9)	2,138 (57.7)
1-Year period prevalence of ALS[c] per 100,000 people (% in male)	2.5 (3.1)	2.6 (3.2)	2.6 (3.1)	2.8 (3.4)	3.0 (3.7)	3.0 (3.6)	3.0 (3.6)
Suicide attempters, n (% male)	12 (66.7)	16 (50.0)	18 (55.6)	21 (52.4)	6 (50.0)	10 (60.0)	11 (45.5)
1-Year period prevalence of suicide attempts, %	0.79	0.99	1.06	1.12	0.29	0.47	0.49

[a]*KCD-6* or *KCD-7* code: G12.20.
[b]*KCD-6* or *KCD-7* code: G12.21.
[c]The prevalence of ALS was calculated as the number of prevalent patients with ALS divided by the total population covered by the Korean National Health Insurance Service for a given year. It was standardized as the Korean midyear population in 2005.
Abbreviations: ALS = amyotrophic lateral sclerosis, *KCD* = *Korean Standard Classification of Diseases*.

populous cities in Korea. By applying algorithms from previous studies[17–19] after a minimal modification, those who had been diagnosed, at least once, with an F code in a psychiatry or neurology department or with F codes belonging to the same group among 8 categories of psychiatric disorders[20] (Supplementary Table 1) during 3 or more outpatient visits in all other departments before the index date were classified as having a history of psychiatric disorder. Those with both a prescription record of psychotropics (Supplementary Table 2) and an F code diagnosis from a psychiatry or neurology department were categorized as having a history of psychiatric pharmacotherapy. Psychiatric hospitalization was defined as an admission to an open or closed ward in a psychiatry department or to a neurology department with an F code diagnosis. We created such an operational definition to avoid overlooking cases in which a neurologist treats psychiatric disorders, such as major depressive disorder, directly without referring them to psychiatry. Only information since 2002 was available for analysis.

Statistical Analyses

In the descriptive analyses, we classified the number of index suicide attempts according to attempt methods along with the annual period prevalence and incidence rate of suicide attempts. A temporal trend in the former was estimated using Poisson distribution. Only incident patients were included in the subsequent analyses. Differences between non–suicide attempters and suicide attempters were compared using Student *t* test (continuous variables) and Pearson χ^2 test or Fisher exact test (categorical variables). Time to index suicide attempt was estimated using the Kaplan-Meier method, and the number of events according to time period was presented. Last, to identify risk factors of index suicide attempt, univariate and multivariable analyses were conducted using the Cox proportional hazards regression model and the competing risk model. A presence of death was considered a competing risk.[21] All risk factors with *P* values < .10 in the univariate analysis were included in the multivariable analysis; psychiatric disorder and hospitalization were separately included in the two models on account of the strong correlation. All statistical analyses were conducted using SAS Enterprise Guide version 7.1 (SAS Institute Inc; Cary, NC). A *P* value < .05 (2-tailed) was considered to be statistically significant.

RESULTS

Among prevalent patients with ALS, 94 attempted suicide from 2011 to 2017 (Table 1). The annual period prevalence of suicide attempts ranged from 0.29% to 1.12%, which did not show a tendency to change with time (*P* = .06). In Table 2, we summarize characteristics of index suicide attempts of all incident patients. During the study, we identified 1,823 men and 1,132 women as incident patients. These patients were followed for a total of 6,083 person-years. Of these incident patients, 23 (1.26%) of the men and 24 (2.12%) of the women attempted suicide at least once during the study period. The most commonly used means for a suicide attempt was intentional self-poisoning (87.2%, 41/47 index suicide attempts).

Comparisons of characteristics between non–suicide attempters and suicide attempters are presented in Table 3. Only psychiatric hospitalization prior to the diagnosis of ALS differed between the groups; it was more frequently observed in suicide attempters (*P* = .01). As shown in Figure 1, 20 of 47 index suicide attempts occurred within 3 months after the diagnosis of ALS; 9 attempts were made during 12–18 months after the diagnosis. The mean ± SD duration since the diagnosis to the index attempt was 10.3 ± 11.3 months. Survival curve was constructed using Kaplan-Meier estimates (Supplementary Figure 1).

In the univariate analyses, psychiatric hospitalization prior to the ALS diagnosis turned out to be the only statistically significant risk factor for suicide attempt (Supplementary Table 3). From the multivariable analysis (Table 4), the hazard ratios for

Table 2.
Characteristics of Incident Patients With ALS

Characteristic	Total	Male	Female
Incident patients, n			
Overall	2,955	1,823	1,132
Familial ALS[a]	174	119	55
Sporadic ALS[b]	2,781	1,704	1,077
Incidence rate of ALS[c] (per 100,000 person-years)			
2012	0.74	0.93	0.55
2013	0.72	0.90	0.55
2014	0.86	1.09	0.62
2015	0.82	1.12	0.53
2016	0.65	0.82	0.49
2017	0.66	0.85	0.48
No. of methods used at index suicide attempt			
Overall	47	23	24
Intentional self-harm (X60–X84)	0	0	0
Event of undetermined intent (Y10–Y34) with an F code diagnosis	0	0	0
Sequelae of intentional self-harm (Y87.0) with an F code diagnosis	0	0	0
Intentional self-poisoning			
Poisoning by nonopioid analgesics, antipyretics, and antirheumatics (T39); poisoning by antiepileptic, sedative-hypnotic, and antiparkinsonism drugs (T42); or poisoning by psychotropic drugs, not elsewhere classified (T43)	14	6	8
Poisoning by drugs, medicaments, and biological substances (T36–T38, T40–T41, T44–T50) or toxic effects of substances chiefly nonmedicinal as to source (T52–T57, T59–T60) with an F code diagnosis	27	13	14
Intentional self-injury			
Open wound of forearm (S51), injury of blood vessels at forearm level (S55), other and unspecified injuries of forearm (S59), open wound of wrist and hand (S61), injury of blood vessels at wrist and hand level (S65), or other and unspecified injuries of wrist and hand (S69) with an F code	4	2	2
Toxic effect of carbon monoxide (T58)	2	2	0
Cumulative incidence of suicide attempts, %	1.59	1.26	2.12
Time interval from ALS diagnosis to index suicide attempt, median (IQR), d	213.0 (27.0–475.0)	205.0 (17.0–442.0)	257.5 (48.0–528.5)

[a]*KCD-6* or *KCD-7* code: G12.20.
[b]*KCD-6* or *KCD-7* code: G12.21.
[c]The incidence rate of ALS was calculated as the number of incident patients with ALS divided by the total population covered by the Korean National Health Insurance Service for a given year. It was standardized as the Korean midyear population in 2005.
Abbreviations: ALS = amyotrophic lateral sclerosis, IQR = interquartile range, *KCD* = *Korean Standard Classification of Diseases*.

psychiatric hospitalization before ALS diagnosis were 3.17 (95% CI, 1.31–7.70; $P = .01$) according to the Cox proportional hazards model and 3.02 (95% CI, 1.32–6.90; $P = .01$) according to the competing risk model.

DISCUSSION

We showed that the annual prevalence of suicide attempts ranged from 0.29% to 1.12% and that there was a 3.02-fold higher risk of suicide attempts among patients with ALS along with a history of psychiatric hospitalization before the ALS diagnosis than in those without it. Index suicide attempts showed the highest frequently within 3 months after diagnosis. These findings are, for the first time, presented to highlight the importance of identifying those at a risk of suicide attempt and paying more attention to those with the risk factor.

A survey on over 100,000 adults from 21 countries showed that the 1-year prevalence of suicide attempts is only 0.3%–0.4%, which is lower than the 1-year prevalence of suicide attempts determined by our study.[22] Moreover, because all of the subjects were hospital visitors enrolled in the NHIS and because approximately 40% of suicide attempters do not seek medical care,[23] it is extremely likely that the prevalence of suicide attempt was considerably underestimated. These findings raise the grave apprehension that patients with ALS are at an increased risk of suicide attempt. In Korea, a series of

Table 3.

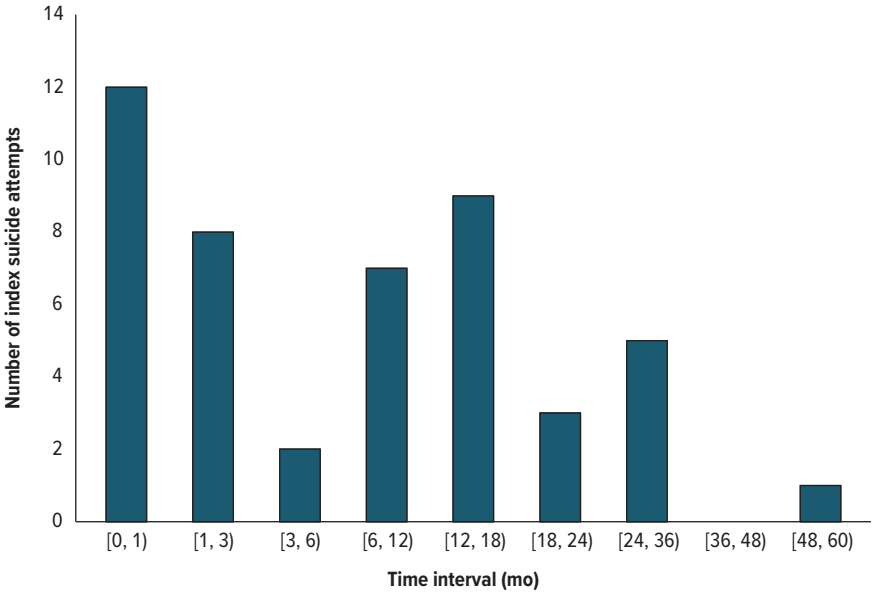
Comparisons of Clinical Characteristics Between Non–Suicide Attempters and Suicide Attempters[a]

Characteristic	Total (N = 2,955)	Non–Suicide Attempters (n = 2,908)	Suicide Attempters (n = 47)	*P* Value
Heritability				.25
Familial ALS[b] n	174	172	2	
Sporadic ALS[c] n	2,781	2,736	45	
Sex				.07
Male	1,823 (61.7)	1,800 (61.9)	23 (48.9)	
Female	1,132 (38.3)	1,108 (38.1)	24 (51.1)	
Age at ALS diagnosis, mean (SD), y	59.5 (13.6)	59.5 (13.6)	61.1 (11.7)	.44
≥ 80	108 (3.7)	105 (3.6)	3 (6.4)	.35
70–79	650 (22.0)	643 (22.1)	7 (14.9)	
60–69	840 (28.4)	821 (28.2)	19 (40.4)	
50–59	743 (25.1)	732 (25.2)	11 (23.4)	
40–49	369 (12.5)	364 (12.5)	5 (10.6)	
< 40	245 (8.3)	243 (8.4)	2 (4.3)	
Household income				.29
High (top 20%)	870 (29.4)	860 (29.6)	10 (21.3)	
Middle (top 21%–60%)	1,171 (39.6)	1,153 (39.6)	18 (38.3)	
Low (bottom 40% or medical aid)	914 (30.9)	895 (30.8)	19 (40.4)	
Region				.75
Metropolitan cities	1,324 (44.8)	1,304 (44.8)	20 (42.6)	
Rural areas	1,631 (55.2)	1,604 (55.2)	27 (57.4)	
Riluzole				.47
No	1,411 (47.7)	1,391 (47.8)	20 (42.6)	
Yes	1,544 (52.3)	1,517 (52.2)	27 (57.4)	
Gastrostomy[d]				.19
No	2,360 (79.9)	2,326 (80.0)	34 (72.3)	
Yes	595 (20.1)	582 (20.0)	13 (27.7)	
Tracheostomy[e]				.08
No	2,428 (82.2)	2,394 (82.3)	34 (72.3)	
Yes	527 (17.8)	514 (17.7)	13 (27.7)	
Psychiatric disorder before ALS diagnosis				.35
No	1,584 (53.6)	1,562 (53.7)	22 (46.8)	
Yes	1,371 (46.4)	1,346 (46.3)	25 (53.2)	
Psychiatric pharmacotherapy before ALS diagnosis				.35
No	1,951 (66.0)	1,923 (66.1)	28 (59.6)	
Yes	1,004 (34.0)	985 (33.9)	19 (40.4)	
Psychiatric hospitalization before ALS diagnosis				**.01**
No	2,728 (92.3)	2,690 (92.5)	38 (80.9)	
Yes	227 (7.7)	218 (7.5)	9 (19.1)	
Suicide attempt before ALS diagnosis				.10
No	2,921 (98.8)	2,876 (98.9)	45 (95.7)	
Yes	34 (1.2)	32 (1.1)	2 (4.3)	

[a]Values are shown as n (%) unless otherwise noted. Significant findings with $P < .050$ are presented in **bold**.
[b]*KCD-6* or *KCD-7* code: G12.20.
[c]*KCD-6* or *KCD-7* code: G12.21.
[d]The mean (SD) time from the diagnosis of ALS to gastrostomy was 15.1 (8.1) and 14.2 (11.8) months for suicide attempters and non-suicide attempters, respectively.
[e]The mean (SD) time from the diagnosis of ALS to tracheostomy was 20.0 (14.9) and 15.0 (12.9) months for suicide attempters and non-suicide attempters, respectively.
Abbreviations: ALS = amyotrophic lateral sclerosis, *KCD* = *Korean Standard Classification of Diseases*.

national suicide prevention measures were implemented in response to the soaring suicide rate in the 2000s.[24] These proactive government efforts seems to have shown effectiveness; since it peaked at 31.7 in 2011, suicide rate per 100,000 individuals decreased to 24.3 until 2017, and it was reported that the initiation of the National Comprehensive Plans of Suicide Prevention is possibly related to the decrease in the overall suicide rate.[24] However, because the annual prevalence of suicide attempt in our study sample did not show either an increasing or a decreasing trend during the study period, we speculate with caution that the national measures might not have been productive enough for ALS patients. Moreover, the effects of the national initiatives differ depending on age

Figure 1.
Number of Index Suicide Attempts Among Incident Patients According to Time Period[a]



[a]The x-axis denotes time interval from the diagnosis of ALS to index suicide attempts in months. The y-axis denotes the number of index suicide attempts. The x-axis labels in the form of [*a*, *b*) indicate greater than or equal to *a* and less than *b*.
Abbreviation: ALS = amyotrophic lateral sclerosis.

and sex,[24] implying that developing tailored intervention for patients with chronic incurable diseases such as ALS at high risk of suicide attempt would be necessary.

The most common method of suicide attempts was intentional self-poisoning; a few patients used intentional self-injury and carbon monoxide poisoning. The proportion of intentional self-poisoning in our study sample is higher than that in the general population who attempted suicide and visited emergency departments, ie, 65.4% according to the 2018 Korea Survey on Suicide[25] and 51.21% according to a US-based study.[26] Because suicidal ideation may lead to suicide attempt, preventing access to potential methods holds off the attempts, and for some people, suicidal impulses, which are often brief, may disappear.[27] In the United Kingdom, morbidity and mortality of paracetamol intoxication decreased after the restriction of pack sizes[28] and the change of packaging[29] to hamper an intake of a toxic amount. Likewise, we regard it reasonable to assume that delaying a collection of toxic amounts of drugs by reducing the number of medicines prescribed at a time can contribute to a reduction in drug intoxication events because it gives a suicidal ideator an opportunity to contemplate and change his/her decision rather than the opportunity to act on impulse. It is customary for patients with ALS or their caregivers to visit a clinic only every few months; consequently, they receive a fairly large number of medicines each time. Thus, one way to limit access to the methods will be to establish a more frequent visit schedule, as long as patients have some physical capability to attempt suicide, to decrease the quantity of medicine stored at home as much as possible. Additionally, involving caregivers actively in the process for preventing suicide attempt by making them manage medicines could be a viable strategy. They can participate in the process by giving support and removing dangerous items.[25]

The risk of suicide attempt after the diagnosis of ALS increased among those with a history of psychiatric hospitalization. This finding is in line with the finding of previous studies that included non-medical samples, ie, hospitalization history increases the risks of suicide attempt[30] and suicide.[31,32] A history of psychiatric disorder is a well-known risk factor of suicide attempt,[33] and particularly psychiatric hospitalization, which can be considered to indicate a poorly controlled psychiatric condition,[34] possibly reflecting severe mental illness, may increase the risk of suicide attempt. To our knowledge, no other study has examined a history of psychiatric hospitalization as a potential risk factor for suicide attempt in patients with severe medical illness, making our finding unique and valuable. Patients with ALS are primarily examined by neurologists from the time of its diagnosis onward. However, neurologists are reported to underrecognize psychiatric disorders in patients with neurologic conditions,[35] possibly because they are undertrained in managing mental disorders[36] or have insufficient consultation time in busy neurology clinics.

Table 4.

Multivariable Analysis for Risk Factors of Suicide Attempts Among Incident Patients With ALS[a]

	Cox Regression Model		Competing Risk Model	
Variable	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Model 1				
Sex				
Male	1		1	
Female	1.50 (0.84–2.68)	.17	1.54 (0.87–2.74)	.14
Psychiatric disorder before ALS diagnosis				
No	1		1	
Yes	1.71 (0.96–3.05)	.07	1.63 (0.93–2.88)	.09
Suicide attempt before ALS diagnosis				
No	1		1	
Yes	3.31 (0.80–13.75)	.10	3.20 (0.77–13.34)	.11
Model 2				
Sex				
Male	1		1	
Female	1.55 (0.87–2.75)	.14	1.59 (0.89–2.85)	.12
Psychiatric hospitalization before ALS diagnosis				
No	1		1	
Yes	3.17 (1.31–7.70)	**.01**	3.02 (1.32–6.90)	**.01**
Suicide attempt before ALS diagnosis				
No	1		1	
Yes	2.65 (0.61–11.41)	.19	2.42 (0.62–9.45)	.20

[a]Significant findings with $P < .050$ are in **bold**.
Abbreviations: ALS = amyotrophic lateral sclerosis, HR = hazard ratio.

Thus, a lengthy, complicated assessment protocol would be impractical. Therefore, a time-saving question, ie, "Have you ever been admitted to a psychiatric or neurologic department because of a psychiatric disorder?" is practical because it does not ask for information on the chief complaint, psychiatric diagnosis, setting of a ward (open/closed), or the type of admission (involuntary/voluntary). Unexpectedly, most of the well-established risk factors of suicide attempt in the general population[33] turned out not to be associated with suicide attempt among patients with ALS. ALS itself is associated with a significantly high risk of a suicide attempt.[37] Thus, the current results partly reflect difficulty in identifying a risk factor in a group that is already at an increased risk of suicide attempt.

In the present study, 42.6% (20/47) of index suicide attempts occurred in the early stage of the disease, ie, within 3 months from the diagnosis of ALS. Our findings are consistent with previous studies that have identified a higher risk of suicide among patients who have recently been diagnosed with ALS.[38] Specifically, one study found that the highest relative risk of suicide occurred during the first year following initial hospitalization for ALS, while another study reported that all deaths by suicide (n = 6) occurred within the first 6 months following an ALS diagnosis.[39] Although riluzole and edaravone have been shown to modestly delay the progression of ALS,[40,41] there is currently no cure or effective treatment for ALS. Neurologists' thorough risk evaluation and, preferably, timely referral to psychiatrists should be made from the early phase, during which this bad news is delivered. Notably, the number of suicide attempters reached the second peak (19.1% [9/47]) during 12–18 months after the diagnosis of ALS. Considering that the mean duration from ALS diagnosis to gastrostomy in our study is 14 months, this period may correspond to the timing of developing moderate-to-severe bulbar impairment such as speech disturbance and swallowing difficulty, eventually leading to loss of autonomy. Many patients with ALS tend to postpone gastrostomy because of psychological difficulties such as depression and anxiety.[42] Patients' perception that enteral feeding via gastrostomy indicates the final stage of disease may arouse negative feelings such as the loss of self-control and independence.[42] Only 12.8% (6/47) of suicide attempts occurred more than 2 years after the diagnosis of ALS. Considering that the mean diagnostic delay for ALS is 9–10 months in Korea,[43] this period is most likely to correspond to ≥ 33 months after the onset of symptoms. A recent study reported that the median time from the onset to King's clinical stage 4 (nutritional/respiratory failure) is 24.8 months, and time to Milano-Torino functional stage 4 (loss of independence in 4 domains) is 27.0 months.[44] The relentless progression of the disease and the consequent physical dependence of most patients in this stage on caregivers could have compromised their ability to attempt suicide.

This study has several limitations. First, detailed information on the clinical characteristics of the patients, such as the date of symptom onset, site of onset, rate of progression, and disease severity, was unavailable. However, the use of Exempted Calculation of Health Insurance for rare, incurable diseases improved the diagnostic validity of ALS. Second, prevalence of suicide attempts may have been underestimated because only those who used medical services at hospitals after a suicide attempt were included; a reason for not visiting a hospital may include no or negligible physical injury or intention to hide suicide attempt. Third, because we defined suicide attempt operationally, a possibility of misclassification bias exists. Owing to the characteristics of the data source, we were unable to assess the accuracy of our diagnosis algorithm. Fourth, because historical information corresponding to only 10–15 years before the index date was available, events that occurred earlier in life could not be analyzed. Fifth, most of the patients were Korean nationals, and thus generalization of our results to other groups should be performed cautiously. Sixth, since the primary focus of this study was to identify a risk factor associated with suicide attempts, the findings cannot be generalized to death by suicide. Seventh, information regarding the psychiatric diagnoses and prescribed medications of patients who attempted suicide was unavailable because

the collection of such data was not planned during the study design stage. Eighth, due to the NHIS dataset's solely providing claims information, we were unable to acquire data regarding whether patients who did not attempt suicide also experienced suicidal ideation or had any interrupted or aborted suicide attempts. Despite the limitations, this study has several strengths. To the best of our knowledge, this study is the first to show the prevalence and the risk factors of suicide attempt in patients diagnosed with ALS. Furthermore, because of the use of the NHID, selection bias was minimized, and bias arising from missing data was nonexistent.

The overall prevalence of suicide attempt was higher in patients with ALS than in the general population. Psychiatric hospitalization before ALS diagnosis increases the risk of suicide attempt. Many attempts occurred during the first 3 months and 12–18 months after the diagnosis. We therefore strongly suggest that neurologists seeing patients with ALS ask all the patients about their history of psychiatric hospitalization, and in the presence of one, we suggest that they provide a thorough in-depth evaluation for suicide attempt risk and cautiously monitor patients during the periods when attempts occur frequently.

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Supplementary Material

Article Title: Suicide Attempts in Patients With Amyotrophic Lateral Sclerosis: An Analysis of the Korean National Health Insurance Database

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DISCLAIMER

Supplementary Table 1. Operational definition of suicide attempts and categories of psychiatric disorders

Methods of suicide attempts	**KCD-6 or KCD-7 codes**
Intentional self-harm	X60–X84
Event of undetermined intent	Y10–Y34 (with an F code[a])
Sequelae of intentional self-harm	Y87.0 (with an F code)
Poisoning by nonopioid analgesics, antipyretics and antirheumatics	T39
Poisoning by antiepileptic, sedative-hypnotic and antiparkinsonism drugs	T42
Poisoning by psychotropic drugs, not elsewhere classified	T43
Poisoning by drugs, medicaments and biological substances	T36-T38, T40-T41, T44-T50 (with an F code)
Toxic effects of substances chiefly nonmedicinal as to source except alcohol and food poisoning	T52-T57, T59-T60 (with an F code)
Toxic effect of carbon monoxide	T58 (with an F code)
Open wound of forearm	S51 (with an F code)
Open wound of blood vessels at forearm level	S55 (with an F code)
Open wound of other and unspecified injuries of forearm	S59 (with an F code)
Open wound of wrist and band	S61 (with an F code)
Open wound of injury of blood vessels at wrist and hand level	S65 (with an F code)
Open wound of other and unspecified injuries of wrist and hand	S69 (with an F code)
Categories of psychiatric disorders	**KCD-6 or KCD-7 codes**
Schizophrenia, schizoaffective disorders, and other nonorganic psychoses	F2x
Bipolar affective disorder and other affective psychosis	F30, F31, or F34.0
Organic disorders and dementia	F0x
Depression and other mood disorders	F32, F33, or F34.1
Anxiety and stress disorders	F4x
Substance use disorders	F1x
Intellectual disability	F7x
Other mental health diagnoses	Other F

Abbreviation: KCD, Korean Standard Classification of Diseases.
[a] F code refers to mental and behavioral disorders.

Supplementary Table 2. List of psychotropics

Classes	Psychotropics
Antipsychotics	
Typical	chlorpromazine hydrochloride, haloperidol, levomepromazine maleate, perphenazine, pimozide, sulpiride
Atypical	aripiprazole, clozapine, olanzapine, risperidone, ziprasidone hydrochloride monohydrate, zotepine, quetiapine fumarate, amisulpride, paliperidone, blonanserin
Mood stabilizers	lithium carbonate, divalproex sodium particle, sodium valproate, valproate magnesium, valproic acid, lamotrigine, carbamazepine
Antidepressants	
SSRI	fluoxetine hydrochloride, fluvoxamine maleate, paroxetine hydrochloride, sertraline hydrochloride, escitalopram oxalate, citalopram hydrobromide
SNRI	venlafaxine hydrochloride, milnacipran hydrochloride, duloxetine hydrochloride, desvenlafaxine succinate monohydrate
NaSSA	mirtazapine
Serotonin modulator	vortioxetine hydrobromide
NDRI	bupropion hydrochloride
TCA	amitriptyline hydrochloride, nortriptyline hydrochloride, clomipramine hydrochloride, imipramine hydrochloride, amoxapine, doxepin hydrochloride
Miscellaneous	trazodone hydrochloride, sodium tianeptine, moclobemide, selegiline hydrochloride, agomelatine
Anxiolytics	
Benzodiazepine	triazolam, alprazolam, bromazepam, chlordiazepoxide hydrochloride, chlordiazepoxide, clonazepam, clobazam, clotiazepam, diazepam, etizolam, flunitrazepam, flurazepam hydrochloride, lorazepam, mexazolam
Non-benzodiazepine	buspirone hydrochloride, tandospirone citrate
Hypnotics	zolpidem tartrate
Cognitive enhancers	donepezil hydrochloride, rivastigmine tartrate, galantamine hydrobromide, memantine hydrochloride, choline alfoscerate
Psychostimulants	methylphenidate hydrochloride, modafinil, armodafinil

Abbreviations: SSRI, selective serotonin reuptake inhibitor; SNRI, serotonin-norepinephrine reuptake inhibitor; NaSSA, noradrenergic and specific serotonergic antidepressant; NDRI, norepinephrine-dopamine reuptake inhibitor.

Supplementary Table 3. Univariate analysis for the risk factors of suicide attempts among incident patients with ALS

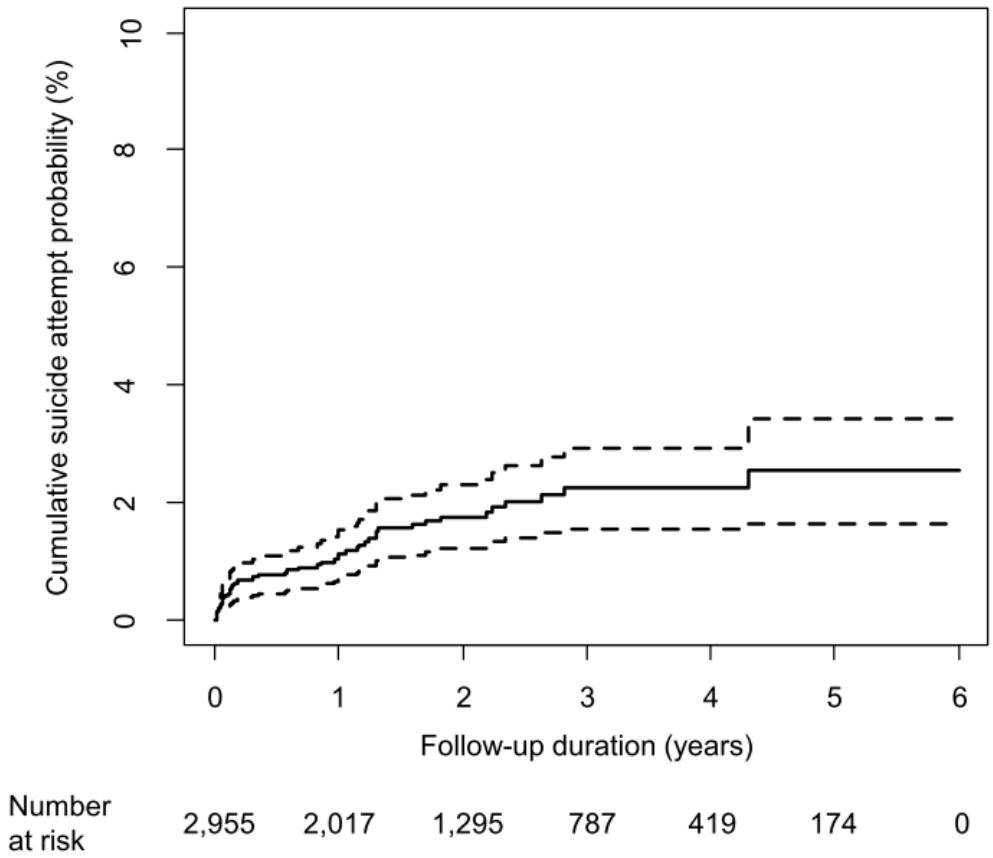
Variables	Crude HR (95% *CI*)	*p* value	Adjusted HR[a] (95% *CI*)	*p* value
Cox proportional hazards model				
Heritability				
Familial ALS[b]	1		1	
Sporadic ALS[c]	1.22 (0.29 – 5.02)	0.79	1.12 (0.27 – 4.63)	0.88
Sex				
Male	1		1	
Female	1.64 (0.93 – 2.91)	0.09	1.60 (0.90 – 2.83)	0.11
Age, y				
≥ 80	1	0.21	1	0.24
70–79	0.32 (0.08 – 1.24)	0.10	0.35 (0.09 – 1.35)	0.13
60–69	0.58 (0.17 – 1.97)	0.38	0.65 (0.19 – 2.22)	0.49
50–59	0.35 (0.10 – 1.26)	0.11	0.39 (0.11 – 1.40)	0.15
40–49	0.30 (0.07 – 1.25)	0.10	0.33 (0.08 – 1.38)	0.13
< 40	0.18 (0.03 – 1.07)	0.06	0.20 (0.03 – 1.22)	0.08
Household income				
High (top 20%)	1	0.30	1	0.22
Middle (top 21–60%)	1.30 (0.60 – 2.81)	0.51	1.44 (0.66 – 3.14)	0.36
Low (bottom 40% or medical aid)	1.79 (0.83 – 3.86)	0.14	1.97 (0.91 – 4.28)	0.09
Region				
Metropolitan cities	1		1	
Rural areas	1.14 (0.64 – 2.03)	0.67	1.12 (0.63 – 2.00)	0.70
Psychiatric disorder before ALS diagnosis				
No	1		1	
Yes	1.86 (1.05 – 3.29)	**0.03**	1.23 (0.68 – 2.21)	0.49
Psychiatric pharmacotherapy before ALS diagnosis				
No	1		1	
Yes	1.44 (0.82 – 2.56)	0.21	1.29 (0.72 – 2.31)	0.39
Psychiatric hospitalization before ALS diagnosis				
No	1		1	
Yes	3.71 (1.57 – 8.73)	**< 0.01**	2.85 (1.37 – 5.95)	**0.01**
Suicide attempt before ALS diagnosis				
No	1		1	
Yes	3.97 (0.96 – 16.36)	0.06	3.53 (0.85 – 14.62)	0.08

Competing risk model				
Diagnosis				
Familial ALS[b]	1		1	
Sporadic ALS[c]	1.18 (0.28 – 4.93)	0.82	1.10 (0.27 – 4.58)	0.89
Sex				
Male	1		1	
Female	1.68 (0.95 – 2.98)	0.08	1.60 (0.90-2.83)	0.11
Age, y				
≥ 80	1	0.36	1	0.37
70 – 79	0.38 (0.10 – 1.47)	0.16	0.42 (0.11 – 1.66)	0.21
60 – 69	0.81 (0.24 – 2.73)	0.73	0.92 (0.26 – 3.19)	0.89
50 – 59	0.52 (0.15 – 1.86)	0.31	0.58 (0.16 – 2.18)	0.42
40 – 49	0.47 (0.111 – 1.94)	0.29	0.52 (0.12 – 2.22)	0.38
< 40	0.30 (0.50 – 1.76)	0.18	0.34 (0.06 – 2.08)	0.24
Household income				
High (top 20%)	1	0.30	1	0.24
Middle (top 21–60%)	1.32 (0.61 – 2.85)	0.49	1.42 (0.65 – 3.10)	0.37
Low (bottom 40% or medical aid)	1.80 (0.84 – 3.88)	0.13	1.91 (0.90 – 4.08)	0.09
Region				
Metropolitan cities	1		1	
Rural areas	1.10 (0.62 – 1.97)	0.74	1.10 (0.62 – 1.96)	0.75
Psychiatric disorder before ALS diagnosis				
No	1		1	
Yes	1.79 (1.01 – 3.16)	**< 0.05**	1.21 (0.68 – 2.14)	0.53
Psychiatric pharmacotherapy before ALS diagnosis				
No	1		1	
Yes	1.40 (0.79 – 2.48)	0.25	1.28 (0.73 – 2.25)	0.39
Psychiatric hospitalization before ALS diagnosis				
No	1		1	
Yes	3.60 (1.51 – 8.38)	**< 0.01**	2.64 (1.26 – 5.53)	**0.01**
Suicide attempt before ALS diagnosis				
No	1		1	
Yes	3.84 (0.92 – 16.12)	0.07	3.50 (0.82 – 14.86)	0.09

Abbreviations: ALS, amyotrophic lateral sclerosis; HR, hazard ratio; CI, confidence interval.

Significant findings with $p < .050$ are in bold fonts.
[a] Adjusted for age and sex.
[b] Korean Standard Classification of Diseases-6 or -7 code: G12.20.
[c] Korean Standard Classification of Diseases-6 or -7 code: G12.21.

Supplementary Figure 1. Kaplan-Meier survival curve for index suicide attempts



The solid line indicates survival curve, and the dashed lines indicate 95% confidence interval.