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Risk of sepsis in patients with amyotrophic lateral sclerosis: a population-based retrospective cohort study in Taiwan

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ABSTRACT

Objectives: Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disease, and sepsis is a frequent cause of death in hospitalised patients. We investigated the relationship between ALS and the subsequent risk of sepsis.

Design: A retrospective cohort analysis.

Setting: Patients with ALSs diagnosed between 2000 and 2010 in Taiwan National Health Insurance Research Database.

Participants: We included 701 and 2804 patients as the ALS and the non-ALS groups, respectively.

Outcome measures: The risk of sepsis was calculated by Cox proportional hazards regression model.

Results: During the follow-up period, the incidence density rates were 77.8 and 11.1 per 1000 person-years in the ALS and non-ALS groups, respectively. After adjusting for sex, age, Charlson comorbidity index score, life-support measures, and β_2-adrenoceptor agonists treatment, the ALS group had a higher risk of sepsis (HR=3.42; 95% CI 2.60 to 4.50) than the non-ALS group. An increase of the risk was observed in patients with ALS receiving life support treatment measures, whereas a decrease of the risk was associated with treatment of β_2-adrenoceptor agonists.

Conclusions: The risk of sepsis is associated with a prior ALS diagnosis, and may be increased by the use of life support measures and decreased by β_2-adrenoceptor agonists.

Strengths and limitations of this study

- Patients included in Taiwan National Health Insurance Research Database are highly representative of the Taiwanese population.
- Amyotrophic lateral sclerosis (ALS) may influence comorbidities, so the Charlson comorbidity index was used to eliminate the confounding factors.
- The absence of data on ALS phenotype limited our ability to associate patients with ALS with certain phenotypes with a higher risk of sepsis.

INTRODUCTION

Amyotrophic lateral sclerosis (ALS), a critical neurodegenerative disease of the motor system,[1 2] is characterised by progressive muscular paralysis that indicates degeneration of motor neurons in the brain and spinal cord.[3] Approximately a half of the patients with ALS die within 2.5 years of symptom onset, frequently due to pulmonary insufficiency, whereas roughly a 10th of patients survive for longer than 10 years.[4] Currently, no cure exists for ALS cases. It is hypothesised that β_2-adrenoceptor agonists may have beneficial effects in treating ALS via restraining protein degradation, promoting protein synthesis, stimulating synthesis and release of neurotrophic factors, regulating microglial and systemic immune function, preserving the structural and functional integrity of motor endplates, and enhancing energy metabolism.[5]

Sepsis is a common cause of death in hospitalised patients, but the treatment is primarily restricted to supporting organ function and administering antibiotics, intravenous fluids and oxygen.[6 7] The number of patients afflicted by sepsis in the USA surpasses 750 000 per year (3.0 per 1000 people).[8] The incidence rate of severe sepsis is 5.07 per 1000 people in Taiwan;[9] 34.4% of the survivors experienced at least one severe sepsis episode later, resulting in 30.2% of the disease burden in 10 years.[10]

The overall deteriorating condition of and invasive treatments administered to patients with ALS may expose patients to a higher risk of sepsis. A previous study showed that patients with ALS were more likely to be hospitalised for sepsis after diagnosis than patients without ALS.[11] Since sepsis exacerbates the morbidity and mortality of patients with ALS, understanding the association

between ALS and subsequent sepsis development is crucial. To evaluate the risk of sepsis associated with ALS, we compared the incidence of sepsis in patients with and without ALS by using data from the Taiwanese National Health Insurance Research Database (NHIRD).

METHODS

Data source

Taiwan National Health Insurance (NHI) is a mandatory single-payer health insurance programme established in 1995. The insurance programme covers 99% of the population of 23.74 million people in Taiwan. The NHIRD is maintained by the National Health Research Institutes (NHRI), Taiwan, providing Taiwanese scientists with access to databases for research purposes.

The NHIRD contains patient data on sex, date of birth, clinical visit and hospitalisation records, prescribed drugs and dosages, and diseases diagnosed according to the codes in the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) version of the 2001. In this study, we used the data sets of the Registry for Longitudinal Health Insurance Database 2000 (LHID 2000) and the Registry for Catastrophic Illness Patient Database (RCIPD). In Taiwan, patients afflicted with 1 of the 30 categories of major illnesses (eg, cancer, chronic mental illness, end-stage renal disease and several autoimmune diseases) can apply for a catastrophic illness certificate. All information that could potentially identify a specific individual patient was encrypted. The data in this study were used in compliance with the regulations of the NHI bureau and the NHRI to maintain the privacy of patients.

Study population

This was a retrospective, population-based cohort study, and figure 1 illustrates the study framework. From the RCIPD, patients older than 20 years who were newly diagnosed with an ALS (ICD-9-CM 335.20) between 1 January 2000 and 31 December 2010 as the ALS group, and the date of application for a catastrophic illness certificate was considered the index date. For every patient with ALS, four patients without motor neuron disease (ICD-9-CM 335.2) were randomly selected from the LHID2000 and frequency matched with the patients in the ALS group according to sex, 5-year age interval, Charlson comorbidity index (CCI) score and index year, as the non-ALS group. The index date for patients in the non-ALS group was a randomly assigned day and month, and the index year was the same year as that of the ALS group. Both groups with missing information (sex and age) and/or with a previous diagnosis of sepsis (ICD-9-CM 038) before index date were excluded from this study. In total, the ALS group comprised 701 patients and the non-ALS group comprised 2804 participants.

The main outcome of this study was the development of sepsis (ICD-9-CM codes 038). All study participants were followed from the index date to the date of end point, that is, until onset of sepsis, withdrawal from the insurance system, or to the end of the year 2011.

Demographic factors contained sex and age (in groups aged 20–44, 45–69, and 70 years and older). According to the inpatient diagnosis of each patient, we calculated the CCI score, which is the sum of the weighted scores of 17 comorbid conditions, as a comorbidity measure. A weight was assigned to each indicated diagnosis, and these weights were summed to generate a total CCI score. To calculate the CCI score, 17 types of comorbidities are classified into categories. Myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, rheumatological disease, peptic ulcer disease, mild liver disease and diabetes mellitus are weighted. (1) Moderate diabetes with chronic complications, hemiplegia or paraplegia, renal disease, any malignancy, leukaemia, and malignant lymphoma are weighted. (2) Moderate-to-severe liver disease is weighted. (3) Acquired immune deficiency syndrome and

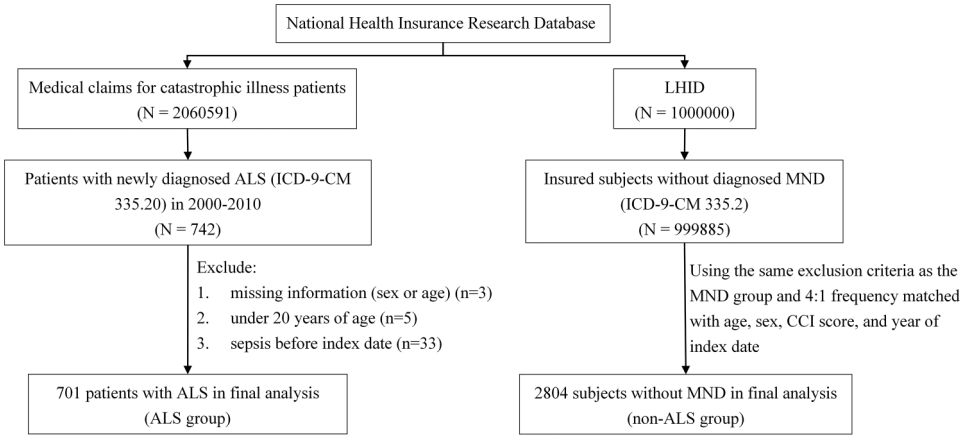

Figure 1 Flow chart for selecting study participants. ALS, amyotrophic lateral sclerosis; CCI, Charlson comorbidity index; ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification; LHID, Longitudinal Health Insurance Database; MND, motor neuron disease.

metastatic solid tumours are weighted.[6 12 13] The CCI score was categorised into three levels: 0, 1–2 and ≥3.

Patients were considered users of β_2-adrenoceptor agonists (including clenbuterol, orciprenaline (metaproterenol), and salbutamol (albuterol)) if they had been dispensed any form of β_2-adrenoceptor agonists for at least 30 consecutive days during the follow-up period. We also considered users of life support treatments, including intensive care unit (ICU) and ventilator use, during the period from the index date through the date of end point.

Statistics

The continuous variables were expressed by means and SDs, whereas categorical variables were expressed by the numbers and percentages. The χ^2 test was used to determine the differences between the two groups in the distribution of the medications therapy and life support measures (including ICU and ventilator use). The incidence density rates of sepsis were calculated for both groups (per 1000 person-years) stratified according to sex, age, and CCI scores. The incidence density rate of sepsis was calculated as the number of sepsis cases divided by the person-years at risk in both groups. We used Poisson regression analysis to measure the incidence rate ratio of sepsis in the ALS and non-ALS groups for these variables. The Kaplan-Meier method was employed to plot the cumulative incidence curves of sepsis during the follow-up period, and the log-rank test was used to assess the differences between the two curves. Univariate and multivariate Cox proportional hazards regression model were used to analyse the association of sepsis-associated risk factors and the occurrence of sepsis. We also used multivariate Cox proportional hazards regression analysis to sex-stratified, age-stratified and CCI score-stratified analysis to investigate the association between ALS and sepsis. Among the three multivariate models used in this study, the first adjusted for sex, age (continuous), CCI score (continuous) and medications therapy. The second model adjusted for sex, age (continuous), CCI score (continuous) and life support measures. The third model adjusted for sex, age (continuous), CCI score (continuous), medications therapy and life support measures. HRs and 95% CIs were calculated to quantify the risk of sepsis.

All data management and statistical analyses were performed using SAS V.9.3 (SAS Institute, Cary, North Carolina, USA). R software (R Foundation for Statistical Computing, Vienna, Austria) was used to plot the Kaplan-Meier survival curves. A two-sided p value <0.05 was considered significant.

RESULTS

As shown in table 1, this study examined 701 patients in the ALS group and 2804 participants in the non-ALS group. Men dominated the study groups (61.5%), and ~80.5% of the patients were younger than 69 years. Patients with ALS were more likely to use medications of β_2-adrenoceptor agonists and to require life support treatment measures (including admission to the ICU and the use of a ventilator), than patients without ALS did.

During the follow-up period, the incidence density rates of sepsis was significantly higher in the ALS group than in the non-ALS group (77.8 vs 11.1 per 1000 person-years, respectively), and the incidence rate ratio (IRR) was 7.04 (95% CI 5.98 to 8.28; table 2). In the subgroup analysis, patients with ALS had a significantly higher IRR of sepsis compared with patients without ALS in both sexes, all age groups, and all groups of CCI scores.

The results of the Kaplan-Meier analysis indicated that the ALS group had a higher cumulative incidence rate of sepsis than did the non-ALS group (log-rank test, p<0.001) as illustrated in figure 2. Multivariate Cox proportional hazards analysis showed that sepsis was independently associated with ALS (table 3). In the three multivariate Cox proportional hazards models showed that patients with ALS had a higher risk of sepsis than participants without ALS (HR=7.80, 95% CI 6.17 to 9.86

Table 1 Baseline demographic factors and comorbidity according to ALS status

	Non-ALS group N=2804		ALS group N=701		
Variables	n	Per cent	n	Per cent	p Value
Sex					
Women	1080	38.5	270	38.5	
Men	1724	61.5	431	61.5	
Age, years					
20–44	432	15.4	108	15.4	
45–69	1824	65.1	456	65.1	
≥70	548	19.5	137	19.5	
Mean (SD)	58.0	(13.0)	58.4	(12.7)	
CCI score*					
0	2072	73.9	518	73.9	
1–2	632	22.5	158	22.5	
≥3	100	3.57	25	3.57	
Mean (SD)	0.42	(0.89)	0.42	(0.89)	
Medications therapy					
β_2-Adrenoceptor agonists†	61	2.18	25	3.57	0.04
Life support measures					
ICU	274	9.77	270	38.5	<0.001
Ventilator use	216	7.70	381	54.4	<0.001

*Charlson comorbidity index including myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, rheumatological disease, peptic ulcer disease, mild liver disease, diabetes mellitus, diabetes with chronic complications, hemiplegia or paraplegia, renal disease, any malignancy, leukaemia, malignant lymphoma, severe liver disease, acquired immune deficiency syndrome and metastatic solid tumours.
†β_2-Adrenoceptor agonists including clenbuterol, orciprenaline (metaproterenol) and salbutamol (albuterol).
ALS, amyotrophic lateral sclerosis; CCI, Charlson comorbidity index; ICU, intensive care unit.

Table 2 Incidence rate ratios of sepsis according to ALS status stratified by sex, age and CCI score

Variables	Non-ALS group			ALS group			IRR (95% CI)
	Event number	Person-years	IR	Event number	Person-years	IR	
Overall	147	13 298	11.1	147	1889	77.8	7.04 (5.98 to 8.28)***
Sex							
Women	45	5113	8.80	46	743	61.9	7.03 (5.37 to 9.21)***
Men	102	8185	12.5	101	1146	88.1	7.07 (5.76 to 8.67)***
Age, years							
20–44	3	2359	1.27	16	416	38.4	30.2 (17.2 to 53.0)***
45–69	72	8609	8.36	104	1213	85.8	10.3 (8.36 to 12.6)***
≥70	72	2330	30.9	27	260	104	3.36 (2.29 to 4.91)***
CCI score							
0	54	10 174	5.31	99	1483	66.7	12.6 (10.3 to 15.3d)***
1–2	72	2807	25.7	40	374	107	4.17 (2.98 to 5.84)***
≥3	21	316	66.4	8	32	248	3.74 (1.67 to 8.37)**

**p<0.01, ***p<0.001.
ALS, amyotrophic lateral sclerosis; CCI, Charlson comorbidity index; IR, incidence density rate, per 1000 person-years; IRR, incidence rate ratio.

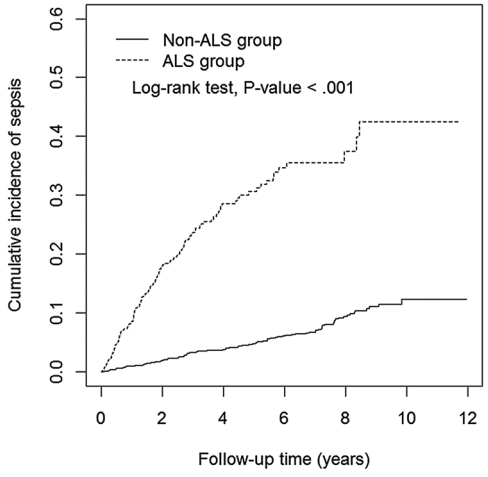

Figure 2 Cumulative incidence curves of sepsis for ALS and non-ALS groups. ALS, amyotrophic lateral sclerosis.

in the model 1; HR=3.38, 95% CI 2.57 to 4.44 in the model 2; and HR=3.42, 95% CI 2.60 to 4.50 in the model 3).

To further assess the robustness of our results, we stratified the study participants based on sex, age group and CCI score (table 4). In the subgroup analysis, patients with ALS were consistently associated with a higher risk of sepsis in both sexes, all age groups and all groups of CCI scores in the three multivariate Cox proportional hazards models.

We observed that patients with ALS who received life support measures had a significantly higher risk of sepsis than did those with no ALS and no life support measures (adjusted HR=23.8, 95% CI 17.3 to 32.6), as shown in table 5. In patients with ALS, we also observed that patients receiving β_2-adrenoceptor agonists therapy had lower risk of sepsis than in patients not receiving β_2-adrenoceptor agonists therapy (adjusted HR=0.42, 95% CI 0.18 to 0.96; table 6).

DISCUSSION

The results indicated that a history of ALS is associated with an increased risk of sepsis. Compared with patients without ALS, patients with ALS were at higher risk of developing sepsis. This was true for women and men and all age groups; the relative risk was greatest among patients aged younger than 45 years. In addition, the risk of sepsis might increase when patients receive life support treatment measures and decrease by β_2-adrenoceptor agonists.

According to the observations in this study, ALS can result in an increased incidence of sepsis, indicating that the pathogenesis of sepsis may be associated with alterations in the immune systems of patients with ALS. As postulated in the Swedish study,[11] patients with ALS frequently die because of infectious complications in the respiratory system that are possibly secondary to ventilatory failure caused by respiratory muscle weakness in the terminal stages of ALS.[14–19] The overall deteriorating condition of patients with ALS, such as malnutrition (in addition to respiratory failure), may expose patients with ALS to a high risk of severe infections, including sepsis. Additionally, patients with ALS may undergo invasive treatments, including tracheostomy or percutaneous endoscopic gastrostomy placement, which can potentially increase the risk of sepsis. One study suggested that severe sepsis represents a failure of homoeostasis resulting from the dysfunction of the neuroendocrine and immune systems.[7] The neuroendocrine system might be impaired in patients with ALS,[20] and this impairment could increase the susceptibility of patients with ALS to the disruption of the organs of the immune system and, hence, sepsis.

Stimulation of the β-adrenergic signalling pathway with β-adrenoceptor agonists has therapeutic potential for muscle wasting disorders including neuromuscular diseases.[21] The selective β_2-adrenoceptor agonist salbutamol might be beneficial in the treatment of sepsis as

Table 3 Cox model measured HRs and 95% CI of sepsis associated with ALS and covariates

	HR (95% CI)			
Variables	**Univariate**	**Model 1**	**Model 2**	**Model 3**
ALS				
No	ref	ref	ref	ref
Yes	6.87 (5.45 to 8.67)***	7.80 (6.17 to 9.86)***	3.38 (2.57 to 4.44)***	3.42 (2.60 to 4.50)***
Sex				
Women	ref	ref	ref	ref
Men	1.40 (1.09 to 1.79)**	1.35 (1.05 to 1.73)*	1.26 (0.98 to 1.61)	1.27 (0.99 to 1.63)
Age				
20–44	ref	ref	ref	ref
45–69	2.55 (1.59 to 4.10)***	2.42 (1.50 to 3.89)***	2.08 (1.29 to 3.36)**	2.13 (1.32 to 3.44)**
≥70	5.41 (3.31 to 8.84)***	4.55 (1.50 to 3.89)***	3.23 (1.94 to 5.37)***	3.35 (2.01 to 5.59)***
CCI score				
0	ref	ref	ref	ref
1–2	2.66 (2.08 to 3.39)***	2.38 (1.86 to 3.05)***	1.75 (1.36 to 2.25)***	1.74 (1.35 to 2.24)***
≥3	6.02 (4.04 to 8.97)***	4.79 (3.15 to 7.28)***	2.75 (1.80 to 4.20)***	2.72 (1.78 to 4.16)***
Medications therapy				
β_2-Adrenoceptor agonists†				
No	ref	ref		ref
Yes	1.77 (1.07 to 2.93)*	0.93 (0.56 to 1.54)		0.63 (0.38 to 1.06)
Life support measures				
ICU				
No	ref			ref
Yes	12.2 (9.61 to 15.5)***		ref	3.47 (2.34 to 5.15)***
Ventilator use			3.43 (2.30 to 5.10)***	
No	1.00			ref
Yes	12.4 (9.79 to 15.8)***		2.17 (1.42 to 3.32)***	2.20 (1.45 to 3.36)***

Model 1 including ALS, sex, age (continuous), CCI score (continuous) and medications therapy.
Model 2 including ALS, sex, age (continuous), CCI score (continuous), ICU and ventilator use.
Model 3 including ALS, sex, age (continuous), CCI score (continuous), medications therapy, ICU and ventilator use.
*p<0.05, **p<0.01, ***p<0.001.
†β_2-Adrenoceptor agonists including clenbuterol, orciprenaline (metaproterenol) and salbutamol (albuterol).
ALS, amyotrophic lateral sclerosis; CCI, Charlson comorbidity index; ICU, intensive care unit.

Table 4 HRs of sepsis according to ALS status stratified by sex, age and CCI score

		ALS group HR (95% CI)			
Variables	**Non-ALS group**	**Crude**	**Model 1**	**Model 2**	**Model 3**
Sex					
Women	ref	7.18 (4.72 to 10.9)***	8.45 (5.51 to 12.9)***	4.25 (2.53 to 7.14)***	4.31 (2.56 to 7.24)***
Men	ref	6.81 (5.15 to 9.00)***	8.00 (6.02 to 10.6)***	3.34 (2.40 to 4.63)***	3.42 (2.46 to 4.75)***
Age, years					
20–44	ref	30.7 (8.90 to 106)***	30.8 (8.93 to 106)***	8.27 (1.89 to 36.2)**	7.80 (1.72 to 35.3)**
45–69	ref	9.90 (7.29 to 13.5)***	10.0 (7.36 to 13.6)***	3.77 (2.60 to 5.48)***	3.77 (2.59 to 5.48)***
≥70	ref	3.43 (2.18 to 5.39)***	3.79 (2.40 to 5.99)***	2.11 (1.30 to 3.45)**	2.35 (1.43 to 3.84)***
CCI score					
0	ref	12.6 (8.98 to 17.6)***	14.3 (10.2 to 20.1)***	4.22 (2.79 to 6.39)***	4.53 (2.99 to 6.86)***
1–2	ref	4.13 (2.78 to 6.14)***	4.63 (3.10 to 6.92)***	2.57 (1.64 to 4.04)***	2.58 (1.64 to 4.06)***
≥3	ref	3.99 (1.71 to 9.33)**	4.09 (1.73 to 9.67)**	3.56 (1.44 to 8.80)**	3.71 (1.47 to 9.34)**

Model 1 mutually adjusting for sex, age (continuous), CCI score (continuous) and medications therapy.
Model 2 mutually adjusting for sex, age (continuous), CCI score (continuous), ICU and ventilator use.
Model 3 mutually adjusting for sex, age (continuous), CCI score (continuous), medications therapy, ICU and ventilator use.
**p<0.01, ***p<0.001.
ALS, amyotrophic lateral sclerosis; CCI, Charlson comorbidity index.

Table 5 Joint effects of ALS and life support measures on risk of sepsis

Variables		N	Event number	IR	HR (95% CI) Crude	HR (95% CI) Adjusted†
ALS	Life support measures‡					
No	No	2502	60	5.03	1.00	1.00
No	Yes	302	87	63.3	12.6 (9.06 to 17.5)***	8.12 (5.74 to 11.5)***
Yes	No	312	25	28.2	5.48 (3.43 to 8.75)***	6.14 (3.84 to 9.83)***
Yes	Yes	389	122	122	23.6 (17.3 to 32.3)***	23.8 (17.3 to 32.6)***

***p<0.001.
†Adjusting for sex, age (continuous), CCI score (continuous) and medications therapy.
‡Life support measures including ICU and ventilator use.
ALS, amyotrophic lateral sclerosis; CCI, Charlson comorbidity index; ICU, intensive care unit; IR, incidence density rate, per 1000 person-years.

Table 6 Incidence density rates and HRs of sepsis according to β_2-adrenoceptor agonists use status stratified by ALS

Variables	N	Event number	IR	HR† (95% CI)
Non-ALS group				
β_2-Adrenoceptor agonists‡				
No	2743	137	10.6	1.00
Yes	61	10	25.3	0.99 (0.52 to 1.89)
ALS group				
β_2-Adrenoceptor agonists‡				
No	676	141	78.8	1.00
Yes	25	6	59.6	0.42 (0.18 to 0.96)*

*p<0.05.
†Adjusting for sex, age (continuous), CCI score (continuous), ICU and ventilator use.
‡β_2-Adrenoceptor agonists including clenbuterol, orciprenaline (metaproterenol) and salbutamol (albuterol).
ALS, amyotrophic lateral sclerosis; CCI, Charlson comorbidity index; ICU, intensive care unit; IR, incidence density rate, per 1000 person-years.

revealed in an in vitro study.[22] Consistent with these reports, our study showed that β_2-adrenoceptor agonists have slight protective effects in patients with ALS for sepsis development (table 5), and supported the hypothesis that β_2-adrenoceptor agonists may provide a novel treatment to reduce the symptoms of ALS.[5]

Our study has several limitations. First, patients with ALS lose weight (even at diagnosis), yet we could not correlate sepsis with malnutrition due to the lack of lifestyle data in the NHIRD. Although the insurance reimbursement policy of NHI is universal and the samples in the NHIRD are highly representative of the Taiwanese population, nutritional status is still likely to affect the distribution of ALS and sepsis in the study sample. Second, ALS may influence comorbidities, so we used the CCI to eliminate the confounding factors caused by ALS. Yet, a bias attributable to the presence of unknown confounders may still exist. Third, the diagnosis records in the NHI claims are primarily used for billing and not verified for scientific purposes. But the high accuracy and validity of the diagnoses of cardiology-related and autoimmune diseases in the NHIRD have been demonstrated,[23] suggesting that the ICD-9-CM codes used in the NHIRD are valid and accurate. Therefore, the data we obtained on the ALS and sepsis diagnoses and the use of life support treatment measures should be reliable. Fourth, the quality of evidence derived from a retrospective cohort study is generally lower than that obtained from randomised trials owing to biases from adjustments for confounding variables. Nevertheless, the use of population-based data from the NHIRD rather than data obtained by self-reports strengthens our study. Fifth, the NHIRD lacks the data about the death of a study participant. Although we can identify the patients who were withdrawn from the insurance programme, the reasons for withdrawal include death, emigration, prison sentence, etc. Since mortality of patients with ALS after diagnosis is so high and the accuracy of this determination impacts the calculation of person-years, the unavailability of accurate survival data could bias our results. Sixth, the absence of data on ALS phenotype (eg, bulbar or respiratory) limited our ability to associate patients with ALS with certain phenotypes with a higher risk of sepsis. The lack of data on the origin of sepsis (such as respiratory tract or urinary) in ALS and non-ALS groups also restricted our understanding in what kind of infections occur in patients with ALS (eg, patients with ALS might have a higher incidence of sepsis related to respiratory infections). There are no data on the pathogens or on clinical practice to avoid sepsis (time to first antibiotic treatment and type, etc). All of these warrant future research to identify the causes and propose prevention strategies of sepsis in patients with ALS history.

Our results indicate that a higher risk of sepsis is associated with ALS in men and women, and this relative risk is highest in patients under 45 years old when compared with patients without ALS. The use of life support measures appears to increase, whereas β_2-adrenoceptor agonists might decrease, the influence of ALS on the subsequent development of sepsis.

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Contributors CW-SL and C-HK were involved in conception and design. All authors were involved in administrative support, data collection and assembly, data analysis and interpretation, and manuscript writing and final approval of the manuscript. C-HK is the guarantor of the paper who assumes responsibility for the integrity of the work as a whole.

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Competing interests None declared.

Ethics approval The Ethics Review Board of China Medical University Hospital in Taiwan approved this study (CMUH-104-REC2-115).

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