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Current Status of the Diagnosis and Management of Amyotrophic Lateral Sclerosis in Korea: A Multi-Center Cross-Sectional Study

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Background and Purpose Recently published, evidence-based guidelines should alter the management of amyotrophic lateral sclerosis (ALS)/motor neuron disease (MND). However, the newest recommendations for ALS/MND therapy are not reflected in actual clinical practice. We sought to evaluate the current status of the diagnosis and management of ALS in Korea.

Methods The Korean ALS/MND research group was organized in 2010, involving more than 50 neurologists from neuromuscular centers in Korea. Participating centers collected data from April to September 2010 on the diagnosis and management of patients with ALS. Data forms from the ALS patient care database, which is a component of the ALS clinical assessment, research, and education program (http://www.outcomes-umassmed.org/ALS/), were modified and used for data collection.

Results In total, 373 sporadic ALS cases from 35 centers were enrolled. The demographic features and clinical findings were similar to those in previous reports from other countries. The mean age at onset was 50-60 years, and a slight male predominance was observed. The enrolled patients predominantly showed focal onset of cervical or lumbosacral symptoms. Only about one-half of the indicated patients (31.4%) received a physician's recommendation for a parenteral gastrostomy, and 18.1% underwent the procedure. Noninvasive ventilation was recommended in 23% of patients, but applied in only 9.5% of them. Tracheostomy was performed in 12.7% of patients.

Conclusions The demographic and clinical features of the diagnosis and management of ALS in Korea are similar to those reported in other countries; however, supportive management, as recommended in evidence-based guidelines, are not yet widely recommended or performed for patients with ALS in Korea. **J Clin Neurol 2012;8:293-300**

Key Words amyotrophic lateral sclerosis, diagnosis, Korea, palliative care, treatment.

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Introduction

Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disease characterized by dominant involvement of the motor system and a grave outcome. No curative treatment is available; therefore, the mainstay of management is primarily supportive and symptomatic.[1] To date only a few standardized therapies have been introduced, and so treatments have been based largely on lower levels of evidence or expert opinion.

Advances have been made in the supportive management of patients with ALS within the past few decades. In addition, evidence-based guidelines were recently published and are

now available for managing patients with ALS.[2-4] Furthermore, there is evidence that a significant improvement in quality of life and survival could be achieved by supportive management, such as noninvasive positive-pressure ventilation (NIPPV) and percutaneous endoscopic gastrostomy (PEG).[5,6] These guidelines provide clinicians with a better rationale for adopting these supportive management procedures and applying them to each properly indicated patient.

The Amyotrophic Lateral Sclerosis Clinical Assessment, Research, and Education (ALS CARE) database was established in North America and is widely used by physicians treating ALS. It provides an opportunity for neurologists to evaluate and systematically follow ALS-related motor neuron disease (MND) and has already provided valuable longitudinal ALS clinical data.[7-9] Importantly, a recent report suggested that this registration improves the diagnostic and therapeutic practices of physicians.[7,9,10] Until now, only one report has been published by a single hospital-based registry in Korea regarding the current status of the diagnosis and management of ALS/MND in Korea.[11] A few years ago there was a proposal to establish a nationwide Korean ALS registry for the same purposes.[12] Many neurologists began to realize the advantage of this registry for both clinical practice and research, and agreed with the need to develop a nationwide prospective ALS registry in Korea.

The aim of the present study was to evaluate the clinical characteristics and supportive care of Korean patients with ALS in a cross-sectional manner. This information would make it possible to identify the current status of ALS diagnosis and management in Korea and compare the results with those from other countries. The second aim of this study was to provide ideas for a working framework to develop a prospective nationwide ALS/MND registry. This would allow the clinical practice of the diagnosis and management of ALS in Korea to be defined and improved.

Methods

Organization of the research network

The Korean ALS/MND research group was organized in February 2010 involving more than 50 neurologists from Korean neuromuscular centers. All of the physicians were Korean neurology specialists whose major field was neuromuscular disorders and who worked either in a university-based hospital or in a tertiary medical center in Korea.

The Korean ALS/MND research group consequently collected data on the management of patients with ALS between April and September 2010. For this purpose the Korean ALS/MND research group developed a questionnaire and conducted a survey by directly contacting patients or by interviewing the patients' primary caregivers.

Diagnosis of ALS and patient enrollment

All patients with ALS were carefully evaluated by an experienced neurologist for the presence of clinical and electromyographic evidence of ALS before being enrolled in the study. We used the El Escorial Criteria (ECC)[13] and its revised form (the Airlie-House criteria) for the ALS diagnosis.[14] We sought to enroll more patients with early-stage ALS in order to increase the diagnostic sensitivity. Thus, we included a "suspected" ALS category, which was dropped from the revised ECC, and included a "laboratory-supported probable ALS" category based on the results of the electrophysiological examination as a novel category for the revised ECC. The Pan-European ALS registry, which is the largest ALS database in the world, recommended and used these same criteria for their enrollment.[15] According to these criteria, an ALS patient was classified as definite, probable, possible, laboratory-supported probable, or suspected ALS based on the impairment of upper motor neurons (UMNs) and/or lower motor neurons and on the number of involved regions (bulbar, cervical, thoracic, and lumbosacral). All patients or caregivers gave their informed consent to participate, and this study was approved by the ethics committees of the respective universities or institutions.

Registration questionnaire

Before conducting the study, a task force team from the ALS/MND research group ("JS Bae, YH Hong, WK Baek, EH Shon, JY Cho, and B-J Kim") developed a registration questionnaire for patient enrollment by modifying data forms from the North American ALS CARE database (http://www.outcomes-umassmed.org/ALS/). The questionnaire was divided into a registration-completion form and a follow-up form. We measured a patient's disability using the ALS Functional Rating Scale (ALS-FRS).

After each patient visit, the data form was registered by the respective neurologist at the outpatient or inpatient department. If the patients could not visit the hospital due to having a poor general condition, a neurologist completed the form based on the information provided by the primary caregiver.

Statistical analyses

Data were analyzed using R software version 2.13.2 (R: A language and environment for statistical computing, Vienna, Austria). Student's *t*-test, the Wilcoxon rank-sum test, and analysis of variance were used to compare groups of continuous variables. Proportions were compared using the chi-square or Fisher's exact tests. In cases of multiple hypothesis testing, the *p* value was adjusted using a Bonferroni correction.

Results

This study was originally designed to be a cross-sectional survey rather than a retrospective review of medical records. The purpose was to collect data that were as complete and accurate as possible. However, data collection was considerably behind schedule after 6 months, so we decided to allow retrospective data collection in order to recruit as many patients as possible during the limited study window.

Data were collected from local investigators at 35 centers. The number of patients from each institution is shown in Fig. 1; approximately 70% of patients came from seven institutions. After excluding duplicates and incomplete or inconsistent data, 434 patients with ALS remained for analyses. The numbers of patients with ALS-like syndrome (n=45), ALS-plus syndrome (n=13), and familial ALS (n=3) were insufficient, and so they were excluded from the analyses.

Data obtained by two different methods (i.e., cross-sectional survey and retrospective data review) were compared; the results are summarized in Table 1. More patients with clinically definite ALS and greater severity, as measured by the revised ALS-FRS, were identified on the cross-sectional side than on the retrospective review of medical records. Other demographic and clinical features did not differ between the two data sets, so further analyses were performed on the combined data set. The major clinical features of the patients with sporadic ALS (n=373) are illustrated in Fig. 2. The disease was mostly focal at onset, with only one or two regions involved in most of the patients (86%). The proportion of patients belonging to the clinically definite and clinically probable groups were 39.4% and 24.1%, respectively, which means that up to 36.5% (i.e., 17.2%, 6.4%, and 12.9% for laboratory-supported probable, possible, and suspected, respectively) did not meet the criteria of clinically definite or probable ALS. Both electromyographic and clinical evidence of UMN dysfunction tended to be less frequently reported, particularly in the bulbar region. An exception was found for the thoracic region, in which electromyographic evidence was most frequently reported, whereas clinical evidence of UMN dysfunction was least frequently reported. Disease severity, as measured by the revised ALS-FRS, did not differ significantly among the five groups of patients with different levels of diagnostic certainty; the median (interquartile range) scores in patients with clinically definite, probable, laboratory-supported probable, possible, and suspected ALS were 30 (21-37), 35 (29-41), 36 (26-42), 44 (10-47), and 37 (24-42), respectively (p=0.11).

The proportions of patients who met the criteria under the published guidelines for supportive interventions including PEG, NIPPV, and tracheostomy, and who underwent these procedures are summarized in Table 2. While the recommendation rates of these supportive interventions tended to be low given the proportion of indications, an even smaller number of patients received these measures in practice. The PEG and NIPPV intervention rates varied considerably among hospitals (p=0.028, 0.016, and 0.34 for PEG, NIPPV, and tracheostomy, respectively; Fig. 3).

Discussion

Major findings

Our results show that the demographic and clinical features of Korean patients with ALS are similar to those of previous reports from other countries[1,16] and a hospital-based study in Korea.[11] The application rate of PEG was similar to that found

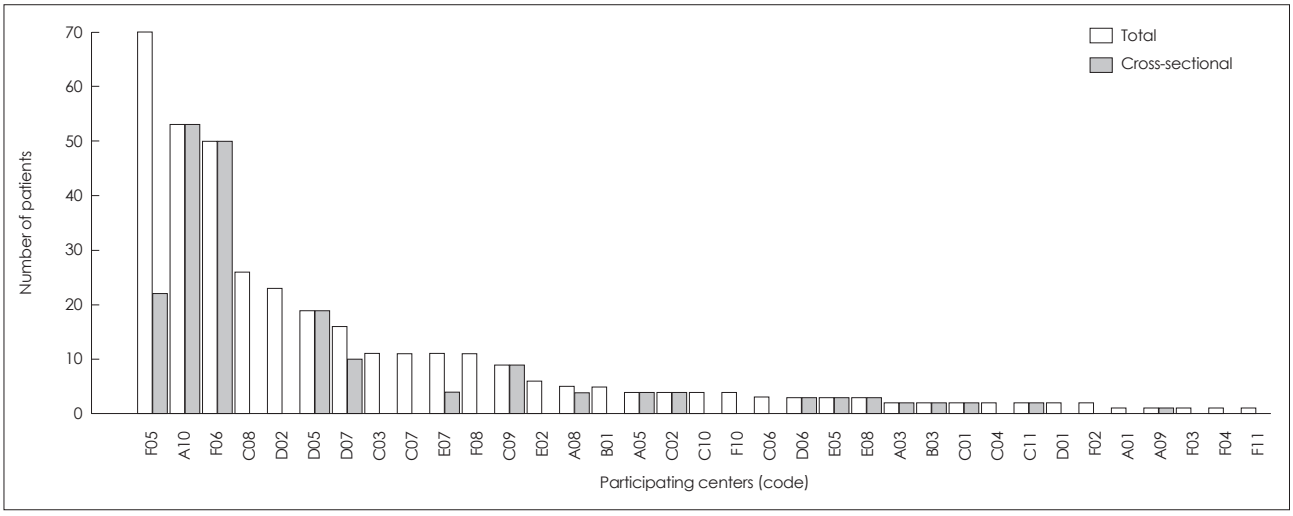

Fig. 1. Patient distribution. Data were collected from 35 institutions by either a cross-sectional survey or retrospective review of medical records. Data were sorted according to the total number of patients (white bars) in descending order. Gray bars represent the cross-sectional survey.

Table 1. Demographic and clinical features of the patients

	Cross-sectional survey	Retrospective review	*p*
Number of patients	197	176	na
Age, years (median, 1Q–3Q)	58 (50–66)	61 (54–69)	0.01
Sex (male : female)	111 : 86	109 : 67	0.32
Body mass index (kg/m^2)†			0.95
Underweight (<18.5)	39 (22.3%)	17 (19.5%)	
Normal (≥18.5, <25)	113 (64.6%)	59 (67.8%)	
Overweight (≥25, <30)	21 (12.0%)	10 (11.5%)	
Obese (≥30)	2 (1.1%)	1 (1.2%)	
Onset region			0.25
Bulbar	68 (20.1%)	55 (20.2%)	
Cervical	151 (44.5%)	136 (49.8%)	
Thoracic	1 (0.3%)	3 (1.1%)	
Lumbar	119 (35.1%)	79 (28.9%)	
Time from symptom onset to diagnosis, years (median, 1Q–3Q)	9.1 (5.1-20.3)	10.1 (5.1-18.2)	0.72
Follow-up duration, years (median, 1Q–3Q)	12.2 (5.1-25.3)	18.2 (6.1-35.5)	0.15
Level of diagnostic certainty†			0.00095*
Definite	89 (45.2%)	58 (32.9%)	
Laboratory-supported probable	50 (25.4%)	40 (22.7%)	
Probable	19 (9.6%)	45 (25.6%)	
Possible	11 (5.6%)	13 (7.4%)	
Suspected	28 (14.2%)	20 (11.4%)	
ALS-FRS score (median, 1Q–3Q)†	31 (22-38)	33 (27-43)	0.0025*
FVC, % of predicted value (median, 1Q–3Q)†	69.0 (44.0–86.5)	67.0 (46.0–80.3)	0.69
Riluzole	60.8%	65.5%	0.43
PEG	14.8%	21.8%	0.12
NIPPV	8.5%	10.6%	0.63
Tracheostomy	10.1%	15.7%	0.16

*p<0.0038 (adjusted using Bonferroni correction), †At the time of the cross-sectional survey, and the most recent data available in retrospectively reviewed cases.
ALS-FRS: Amyotrophic Lateral Sclerosis Functional Rating Scale, revised, FVC: forced vital capacity, na: not applicable, NIPPV: noninvasive intermittent positive-pressure ventilation, PEG: percutaneous endoscopic gastrostomy, 1Q-3Q: interquartile range.

in the ALS CARE database;[7] however, respiratory support in Korea was primarily invasive (i.e., tracheostomy) rather than noninvasive (i.e., NIPPV).[5] Considering the recent indications for these interventions, their recommendation rates tended to be low. In addition, application rates of these management procedures varied considerably among major centers. Given that quality of life and survival can be improved by NIPPV and PEG,[5,6] the lower rate of adoption of these procedures in Korea may be due to the individual decisions of the respective neurologists, the environment of each hospital, or to patient personal or cultural preferences rather than by objective evidence-based guidelines.

Demographic and clinical features

The incidence of sporadic ALS in the 1990s was reported to be 1.5-2.7 per 100000 population/year (average 1.89 per 100000/year) in Europe and North America.[17] The point prevalence is 2.7-7.4 per 100000 (average 5.2 per 100000) in Western countries. Although our study included most of the large centers that manage and follow patients with ALS in Korea, we could not estimate the aforementioned classical epidemiological parameters. However, some of our demographic findings were similar to those of previous reports.[17] A consistent finding in previous reports is that there is a slight predilection toward males being affected by ALS, with a male : female ratio of about 1.5 : 1. We also found a slight male predominance among our patients. Nevertheless, more recent data suggest that the sex ratio might be approaching unity.[1,17] Some reports have identified that the mean age at onset for sporadic ALS varies between 55 and 65 years, with a median age of onset of 64 years.[16] Our findings also showed that the 50s and 60s were the most frequent ages for symptom onset.

Some limitations should be considered when investigating ALS epidemiology. Individuals with ALS who did not seek me-

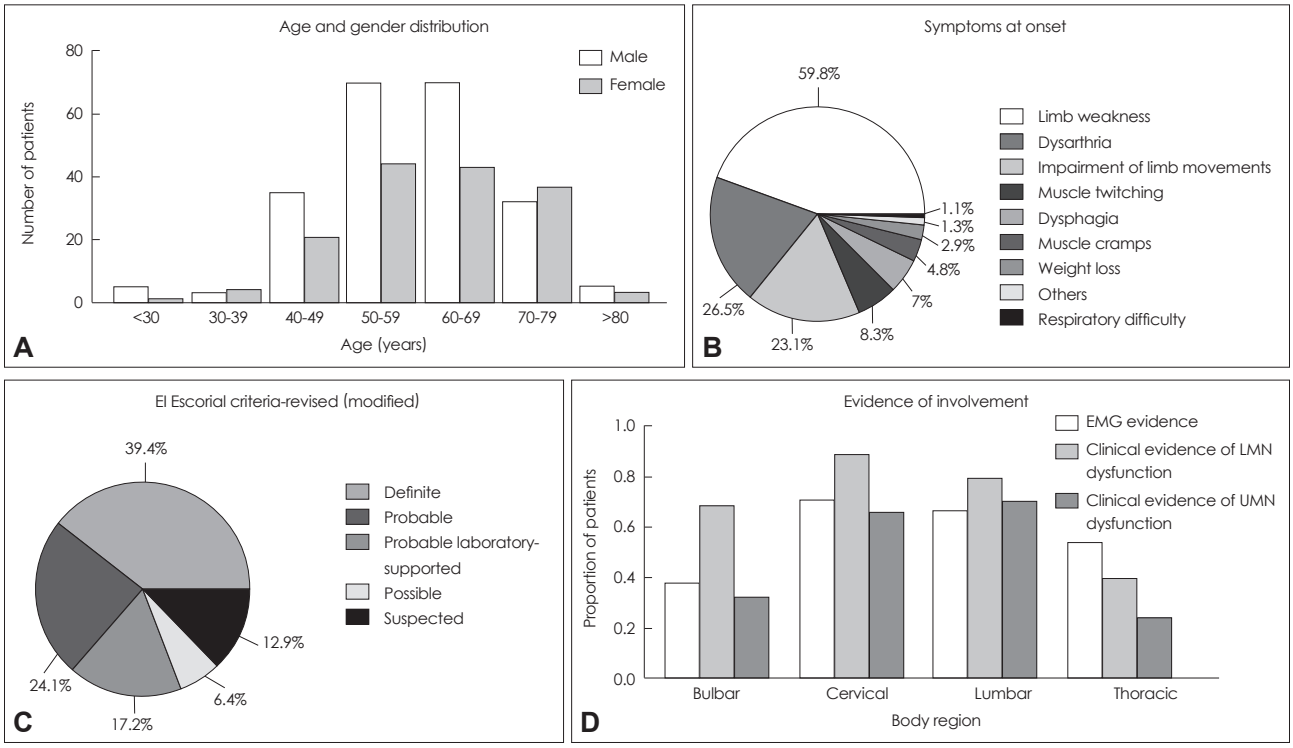

Fig. 2. Clinical features of 373 patients with sporadic amyotrophic lateral sclerosis (ALS). Age and sex distributions (A), first symptoms at onset (B), level of diagnostic certainty according to the revised (and modified) El Escorial Criteria (C), distribution of clinical evidence for upper and lower motor neuron dysfunction, and distribution of electromyographic evidence for lower motor neuron loss across four regions (D).

dical attention or who died prior to establishing the diagnosis, by definition, would not have been enrolled in any study. This is of particular concern among older patients with neurodegenerative disorders. For example, door-to-door surveys have shown that almost 40% of patients with Parkinson's disease remain undiagnosed even in countries with public healthcare systems.[18] ALS is a less common disease that is even more difficult to diagnose than Parkinson's disease, and hence collecting epidemiological data is likely to be more inaccurate than for other neurodegenerative disorders.

To overcome this challenge, several population-based registries were established in the early 1990s to prospectively survey the epidemiology of ALS in defined geographical regions.[8,15] The ALS CARE database, which is a clinical registry using a simple questionnaire, is another distinct multicenter-based registry in North America.[9,10] These approaches have been considered as alternatives that can substitute for population-based epidemiological research and are now widely used. In fact, our study was originally planned as a framework to establish a nationwide ALS registry in Korea. This registry can be used to identify ALS epidemiological information in Korea.

Nutritional palliative care

Nutritional support might be one of the most commonly overlooked aspects of ALS patient care. In fact, malnutrition increases the relative risk of death by almost eightfold in patients with ALS.[19] Severe malnutrition is also associated with muscle atrophy, muscle weakness, and diaphragmatic weakness.[20-22] Therefore, aggressive nutritional care is essential for patients with ALS. Our results showed that about 20% of patients were underweight, as evaluated by the body mass index. We did not evaluate whether special nutritional support was adopted for these 20% of patients. It is reasonable to assume that lengthy evaluation and management is not widely practiced and might be difficult in the Korean hospital and insurance system. Some hospitals in Western countries provide multidisciplinary clinics for ALS care, and this approach has been reported to improve the quality of life in patients with ALS.[23] Physicians caring for patients with ALS should recognize this problem as early as possible, since correcting it can influence the overall outcome.

PEG was recommended in the American Academy of Neurology guidelines for patients with symptomatic dysphagia to minimize the procedural risk when forced vital capacity has not yet declined to <50% of the predicted value.[4] According to our results, PEG was performed in 18.1% of patients. This percentage is slightly higher than that of the ALS CARE database (16% of patients received PEG).[7] It remains uncertain whether physicians do not recommend PEG because of a lack of evidence of sufficient benefit, physician bias, a center's lack of resources, potential complications of the procedure, or simply

that patients are reluctant to undergo such a procedure. However, one report demonstrated a marked variability in the use of PEG among ALS clinics. That report suggested that certain factors bias a clinic or physician toward the increased use of PEG.[6] Although there was some positive impact, the ALS CARE database suggests that PEG does not affect survival.[7] However, PEG may have been performed too late to show survival benefits.[6] Therefore, a future workup is needed to clarify this issue.

Respiratory palliative care

NIPPV has been associated with improved survival in patients with ALS and has been widely recommended.[24-26] It can also improve patient symptoms[27] and health-related quality of life.[28,29] However, it appears that a considerable proportion of patients do not receive NIPPV, even in Western countries. Numerous reasons for this have been proposed, including physician attitudes,[30] cost,[31] caregiver burden,[4] and the complete paralysis and loss of communication that ultimately occurs in these patients.[32] Compared to the ALS CARE database, our results showed that a relatively small proportion of patients with ALS received NIPPV (16%[5] vs. 9.5%). In addition, according to the ALS CARE database, NIPPV has become the most widely used form of ventilator support for patients with ALS in North America, with only 2% receiving invasive mechanical ventilation. However, our data show that 11% of patients underwent a tracheostomy, indicating that invasive respiratory support is still the most common procedure in Korea. In contrast, the application rate of NIPPV was remarkably variable, even among large ALS centers in Korea. However, one possible explanation for this finding is the atypically high proportion of patients with lower diagnostic certainty in our data: 36.5% of patients did not meet the criteria of clinically definite or probable ALS. Furthermore, about 20% of patients were possible or suspected ALS, and clinicians might be more conservative in their therapeutic practice when the diagnosis is uncertain.

Table 2. Supportive care including PEG, NIPPV, and tracheostomy

Management	Number of patients (%)*
PEG	
Indication	
Dysphagia	127 (56.5%)
Significant weight loss	61 (26.2%)
Declining pulmonary function	63 (31.7%)
Recommendation	110 (31.4%)
Insertion	63 (18.1%)
NIPPV	
Indication	
Dyspnea	127 (37.8%)
Daytime sleepiness	41 (14.5%)
Nocturnal awakening	37 (14.0%)
Morning headache	28 (10.2%)
Recommendation	51 (23.0%)
Intervention	33 (9.5%)
Tracheostomy	
Discussion as an elective procedure	29 (18.0%)
Intervention	45 (12.7%)

*To calculate the proportion (%), the number of patients was divided by the total response count, which varied among items.
NIPPV: noninvasive intermittent positive-pressure ventilation, PEG: percutaneous endoscopic gastrostomy.

We did not analyze other modalities requiring supportive management, such as depression, sleep disturbances, spasticity, or sialorrhea. The ALS CARE database emphasizes the importance of those additional management procedures and demonstrated significant changes following their application.[7]

Conclusions

This is the first nationwide, multicenter study of the demographic and clinical findings of ALS in Korea, and is the first to provide information on how often NIPPV and PEG are used for this devastating disease in Korea. This study has re-

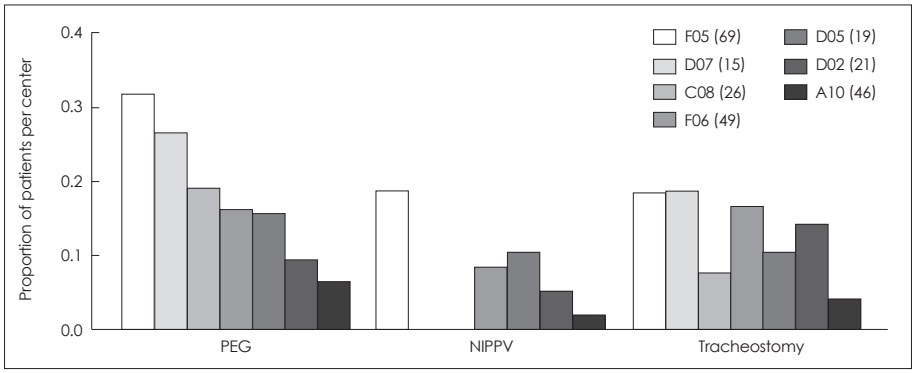

Fig. 3. Rates of percutaneous endoscopic gastrostomy (PEG), noninvasive intermittent positive-pressure ventilation (NIPPV), and tracheostomy. Seven institutions that contributed the greatest number of patients were chosen and are represented by different colors. Numbers within parentheses indicate the number of patients whose data were collected in the corresponding institution. The rates of supportive intervention varied between the centers, including of PEG and NIPPV (p=0.028 and 0.016, respectively).

vealed that supportive management for patients with ALS remains insufficient and is usually introduced by subjective experience rather than objective guidelines. These findings highlight the unmet clinical need, and give physicians tools to better understand the guidelines, evaluate an appropriate patient population, and implement (when possible) to improve overall care and benefit for ALS patients.

One of the most important outcomes of the ALS CARE database project is a favorable change in physician behavior. According to recent reports, physicians were influenced to provide supportive care for patients with ALS behavior after collecting data for this registry.[7,9,10] The Korean ALS/MND research group designed and established a nationwide ALS registry as a prospective longitudinal database,[12,33] and it has been operated and used as a prospective multicenter cooperative hospital-based registry of Korean ALS. It is thus now possible to evaluate both basic information regarding the current status of ALS diagnosis/treatment and the favorable effects of the treatment procedures.

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Conflicts of Interest

The authors have no financial conflicts of interest.

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