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ORIGINAL COMMUNICATION

Nationwide survey of 780 Japanese patients with amyotrophic lateral sclerosis: their status and expectations from brain–machine interfaces

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Abstract

Background Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disease that causes eventual death through respiratory failure unless mechanical ventilation is provided. Brain–machine interfaces (BMIs) may provide brain control supports for communication and motor function. We investigated the interests and expectations of patients with ALS concerning BMIs based on a large-scale anonymous questionnaire survey supported by the Japan Amyotrophic Lateral Sclerosis Association.

Methods We surveyed 1918 patients with ALS regarding their present status, tracheostomy use, interest in BMIs, and their level of expectation for communication (conversation, emergency alarm, internet, and writing letters) and movement support (postural change, controlling the bed, controlling household appliances, robotic arms, and wheel chairs).

Findings Seven hundred and eighty participants responded. Fifty-eight percent of the participants underwent tracheostomy. Approximately, 80% of the patients experienced stress or trouble during communication. For all nine supports, > 60% participants expressed expectations regarding BMIs. More than 98% of participants who underwent tracheostomy expected support with conversation and emergency alarms. Participants who did not undergo tracheostomy exhibited significantly greater expectations than participants with tracheostomy did regarding all five movement supports. Seventy-seven percent of participants were interested in BMIs. Participants aged < 60 years had greater interest in both BMIs.

Interpretation This is the first large-scale survey to reveal the present status of patients with ALS and probe their interests and expectations regarding BMIs. Communication and emergency alarms should be supported by BMIs initially. BMIs should provide wide-ranging and high-performance support that can easily be used by severely disabled elderly patients with ALS.

Keywords Brain machine interface · Amyotrophic lateral sclerosis · Questionnaire survey

Yu Kageyama, Xin He, and Masayuki Hirata have contributed equally to this work.

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Introduction

ALS is a progressive neurodegenerative disease that affects motor neurons and causes progressive muscle weakness and eventual death through respiratory failure within 3−4 years, unless patients are supported by mechanical ventilation [1]. The proportion of patients with ALS in Japan receiving mechanical ventilation is higher than that in other countries due to differences in cultural practices and health insurance systems. When invasive ventilator support is resorted to for life prolongation, assistive communication devices become indispensable. However, these devices fail as the condition progresses to a total locked-in state (LIS), as presently available assistive communication devices are controlled by a switch based on sensors detecting body movement or muscle activity [2–5].

A brain–machine interface (BMI) is a technology that utilizes information directly from the brain, offering an assistive technology that eliminates the need for movement or communication. BMIs may be able to provide a new communication channel to individuals with severe neurological diseases, including ALS, and movement support for tetraplegia caused by severe spinal cord injury or cerebrovascular disease [6–10]. In recent BMI studies, high-performance neuroprosthetic control was achieved by individual with tetraplegia [7, 8]. A fully implantable BMI device provided a locked-in patient with ALS with communication support for as long as 28 weeks. Even if patients with ALS are supported by mechanical ventilation, their condition eventually deteriorates to a total LIS. Because of the devastating incurability of the disease, loneliness caused by social isolation, low quality of life (QOL), and the sense of burden to caregivers, only 3–5% of patients with ALS receive tracheostomy positive pressure ventilation (TPPV) in North America and many European countries [11, 12]. However, in Japan, as many as 30–45% of patients with ALS undergo TPPV, mainly due to cultural differences [11, 12]. Therefore, it is important to support patients with ALS using BMIs. However, the interest of patients in BMIs and the types of support they expect from BMIs are unclear. Thus, understanding the present status of patients' daily inconveniences and their interests and expectations from BMIs is indispensable for the technological development and clinical application of BMIs.

There are few studies reporting the interest of patients with ALS in BMIs. Huggins et al. [13] conducted a telephone survey to assess the opinions of mildly affected patients with ALS concerning BMI designs. Lahr et al. [14] elucidated that the group of ALS patients was especially open to the concept of BMIs among paralyzed patients. We preliminarily reported a questionnaire survey of 37 patients with severe ALS [15]. We found that nearly 90% participants felt difficulties with communication. They expected a wide range of support from BMIs. However, the study population was small and focused on severely affected patients. Therefore, in this study, we aimed to clarify the present status of patients with ALS and reveal the interests and expectations of the majority of patients with ALS concerning BMIs using a nationwide questionnaire survey with high statistical reliability to develop BMIs that meet the needs of patients.

Methods

Study design and participants

In this study, we received the full support and cooperation of the families of patients with ALS and the Japan ALS Association (JALSA). We conducted an anonymous, mail-back questionnaire survey for all of the 1918 patients with ALS registered at JALSA. Regarding the content of the questionnaire, we consulted neurologists and coordinators specializing in ALS, researchers of neuroethics, and JALSA commissioners. The questionnaire was based on our previous preliminary survey [15] for severely affected patients with ALS and was further simplified to be less stressful and could be completed in approximately 10 min. The cover letter explained what BMIs are, their functions, and the purpose of the survey. We also mailed comprehensive digital video discs regarding BMIs. We instructed study participants to answer the questions after watching the video.

The questionnaire, comprising two parts, included 40 questions (Supplementary data 1). The first part contained general demographic questions about the participants, including age, gender, and who answered the questionnaire. It also inquired about disease severity (writing, conversation, and movement) and medical procedures in use [aspiration, tracheostomy, and supportive ventilation, namely non-invasive positive pressure ventilation (NIPPV) and TPPV]. In addition, we asked about assistive communication devices in use and the use of personal computers (PCs).

In the second part, we assess the patients' interest in invasive and non-invasive BMIs. We evaluated their interest in BMIs to choose which functions they expect from the following nine supports: wheel chairs, emergency alarms, controlling household appliances, robotic arms, writing letters, postural change or excretion, Internet or e-mail, conversations, and controlling the bed. Then, we determined their expectations for each support using multiple-choice questions (highly expected/moderately expected/not much expected/not expected). Free-style questions about expectations for and anxieties about BMIs were also included.

Statistical analysis

We used a simplified revised Amyotrophic Lateral Sclerosis Functional Rating Scale (ALSFRS-R) to score disease severity (Supplementary data 2) [16, 17]. The scale contained questions on writing, conversation, movement, tracheostomy, and supportive ventilation. The scores ranged from 3.0 to 24.0, with 3.0 indicating most serious. We scored the participants' expectations from 1 to 4 (1 for not expected, 2 for not much expected, 3 for moderately expected, and 4 for highly expected). We compared the expectations from BMIs between patients with ALS with and without histories of tracheostomy using the Mann–Whitney–Wilcoxon test. We also evaluated the factors affecting the interest in non-invasive and invasive BMIs using multinomial logistic regression. Participants' interest in non-invasive, invasive, or both BMIs was used as a response outcome, and the participant's background (gender, age, responder, PC usage, and history of tracheostomy) was used as a covariate. Demographic values were reported as the mean ± standard deviation. Statistical analyses (Mann–Whitney–Wilcoxon's test and multinomial logistic regression) were conducted using standard statistical analysis software (JMP Pro 10; SAS Institute, Cary, NC, USA). A threshold of $P < 0{\cdot}05$ was used for statistical inference.

Ethical approval

The present study was conducted in cooperation with the Osaka Intractable Diseases Medical Information Center (OIDMIC) and JALSA under the approval of the institutional review board of the Osaka University Hospital (No. 09008-4). A questionnaire was mailed to all patients with ALS registered at JALSA. Anonymity was guaranteed. The investigators in the Osaka University Medical School were blinded to participant selection and personal information.

Results

General questions

Patient profiles

Of 1918 patients to whom questionnaires were sent, 780 [40.7%; men, 461; women, 311; unknown, 8; age 19–85 years (64.1 ± 10.3 years)] completed the survey (Table 1). Three hundred and forty-seven questionnaires (44.6% patients) were answered by the patients themselves, 393 questionnaires (50.4%) were completed by family members who assumed the patients' intentions, and the respondents were not specified for 40 questionnaires (5.1%).

Table 1 Patient profiles

	Number of patients
Mail-in respondents	1918 780 (40.7%[b])
Age (years ± SD)	64.1 ± 10.3[c]
Male/Female	461/319 (59.1/40.9%[d])
Responder	
Patient	196 (25.1%[d])
Patient and family or caregiver[a]	151 (19.4%[d])
Family or caregiver	393 (50.4%[d])

[a]Patients answered with the assistance of their family or caregiver

[b]A percentage for 1918 mail-in subjects

[c]Means ± SD

[d]Percentages for 780 respondents

In general, disease severity was high in most of the participants. For each of the three questions regarding disease severity (writing, conversation, and movement), approximately 60% of patients chose the answers indicating the most serious severity. Four hundred and ninety-one patients (62.9%) could not point at words using their fingers, 458 (58.7%) were nearly or completely unable to speak, and 463 (59.4%) were completely unable to move their legs (Table 2, Supplementary Fig. 1). The scores of our simplified ALSFRS-R for the 624 participants who completed all the questions ranged from 3.0 to 24.0 (median, 7.0; mean, 10.0 ± 6.8) (Fig. 1). In 335 patients (53.7%), the score of the simplified ALSRS-R was no more than 8. Five hundred and two patients (64.4%) underwent oral or pharyngeal aspiration (Supplementary Fig. 2), 450 (57.7%) underwent tracheostomy, and 361 (46.3%) were supported by NIPPV (8.8%) or TPPV (36.9%).

Communication

Two hundred and fifty-seven patients (32.9%) were able to communicate vocally, 235 (30.1%) used assistive communication devices, and 232 (29.7%) used a letter board (Supplementary Fig. 3). Communication was smooth in 432 patients (55.3%), restricted in 237 patients (30.4%), and impossible in 149 patients (19.1%) (Supplementary Fig. 3).

Approximately, 80% of the patients experienced some stress or trouble during conversation (Supplementary Fig. 3). Three hundred and thirteen patients (40.1%) experienced stress while communicating due to prolonged time consumption, and 325 (41.6%) found communication laborious (Supplementary Fig. 3). Two hundred (85.1%) out of 235 patients who used assistive communication devices available at present had some trouble using the devices (Supplementary Fig. 4). One hundred and forty-seven patients (62.6%) complained of difficulties in

Table 2 Severity of ALS patients

Feature		Number of patients (%[b])
Performance	The most frequently selected answer	
Writing	Unable to point at words by fingers	491 (62.9)
Conversation	Nearly or completely unable to speak	458 (58.7)
Walking or moving	Completely unable to move legs	463 (59.4)
Medical support		Yes/No (%[b])
Oral or pharyngeal aspiration		502/258 (64.4/33.1)[c]
Tracheostomy		450/319 (57.7/40.9)[c]
Supportive ventilation (artificial ventilation or BiPAP[a])		361/387 (46.3/49.6)[c]

[a]BiPAP; biphasic positive airway pressure

[b]Percentage for 780 respondents

[c]There are patients who did not answer these questions; 20, 11, 32, respectively

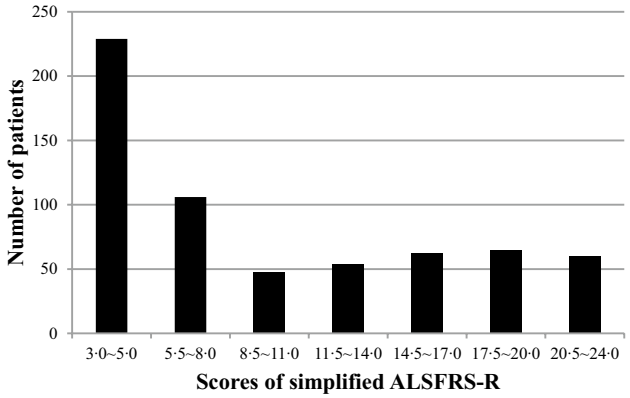

Fig. 1 Distribution of scores of the simplified revised Amyotrophic Lateral Sclerosis Functional Rating Scale (ALSFRS-R) among the patients. A lower score indicates a more severe condition. We divided the participants into a severe group (score 3.0–8.0) and a relatively mild group (score 8.5–24.0)

troubleshooting when devices did not work as intended, 124 (52.8%) complained of difficulties in operating them, and 107 (45.5%) complained of difficulties in replacing the input methods of assistive communication devices to fit it according to the progression of the symptoms (Supplementary Fig. 4).

Personal computers

Three hundred and sixty-four participants (46.7%) answered that they frequently or sometimes used PCs (Supplementary Fig. 5). They used PCs to obtain information (64.3%) or send e-mails (61.0%). By contrast, 400 participants (52.3%) answered that they never or rarely used PCs. Of these non-PC users, 193 (48.3%) attributed this lack of use to their own physical disability.

Expectations from BMIs

For each of the nine supports, at least 60% participants expressed strong or moderate expectations. Nearly, all participants had moderate or high expectations for conversation and emergency alarms (conversation: 98.7% with tracheostomy and 96.0% without tracheostomy, emergency alarm: 98.6% with tracheostomy and 93.2% without tracheostomy) (Fig. 2). Essential communication support (conversation and emergency alarm) was more highly expected than high-performance communication support (Internet/e-mail and writing letter) by participants with as well as those without tracheostomy.

Over 80% of participants without tracheotomy had moderate or high expectations for each of the five movement supports (bed control, 93.6%; body position control, 92.4%; lighting control, 90.0%; robotic control, 82.6%; and wheel chair, 81.5%). Movement support associated with physical care (e.g., support for postural change or excretion or controlling the bed) was more highly expected than high-performance movement support (robotic arms and wheel chairs) by participants with as well as those without tracheostomy.

Differences in expectations between patients with and without tracheostomy

The number of participants with tracheostomy having moderate or high expectations for conversation ($P=0.02$) and emergency alarms ($P=0.001$) was significantly higher than that of those without tracheostomy. The number of participants without tracheostomy having moderate or high expectations for all five movement supports was significantly higher than that of those with tracheostomy (Fig. 2).

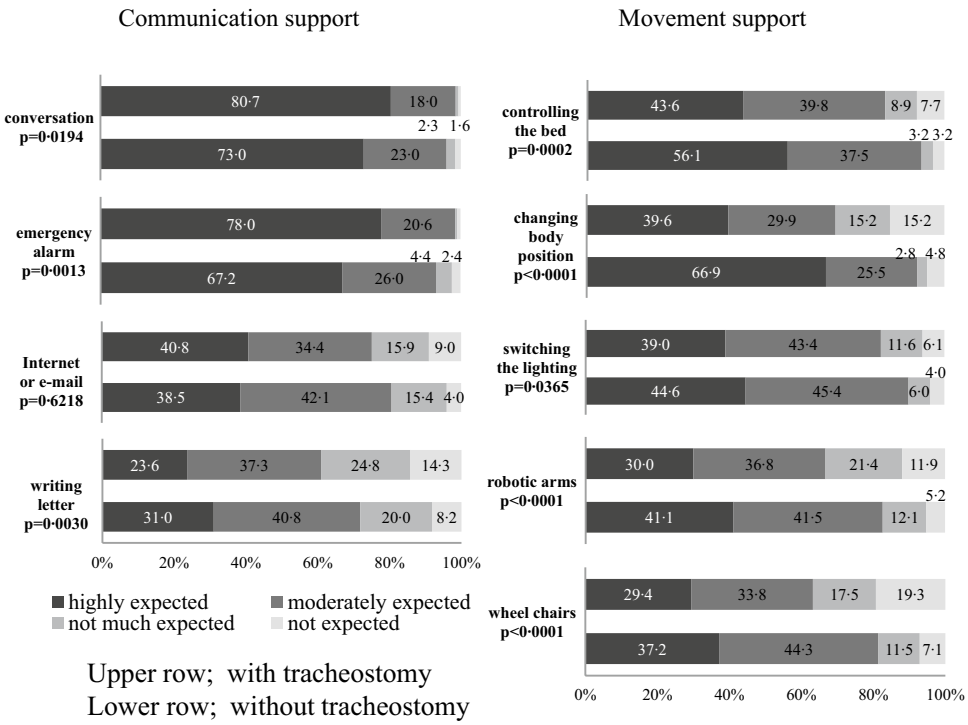

Fig. 2 Interest in brain–machine interfaces (BMIs). Invasive; interested only in invasive BMIs. Both; interested in both invasive and non-invasive BMIs. Non-invasive; interested only in non-invasive BMIs. Neither; interested in neither invasive nor non-invasive BMIs. The percentage indicates the proportion of participants who selected the answer among 780 responders

Invasiveness of BMIs and factors affecting interest in BMIs

Six hundred and three patients (77.3%) were interested in BMIs. Of these, 225 patients (28.8%) had interest in non-invasive BMIs, 151 patients (19.4%) in invasive BMIs, and 227 patients (29.1%) in both BMIs (Fig. 3). Participants aged < 60 years were significantly more interested in both invasive ($P = 0.03$), non-invasive ($P = 0.04$), and both BMIs ($P = 0.001$) than older patients (Fig. 4). Frequent PC users displayed a mild tendency toward greater interest in invasive ($P = 0.16$) and non-invasive BMIs ($P = 0.20$). Participants with tracheostomy also exhibited a mild tendency to be interested in non-invasive BMIs ($P = 0.15$). There was no significant difference in interest in non-invasive and invasive BMIs based on the gender of the patients and whether or not they responded to the questionnaire themselves.

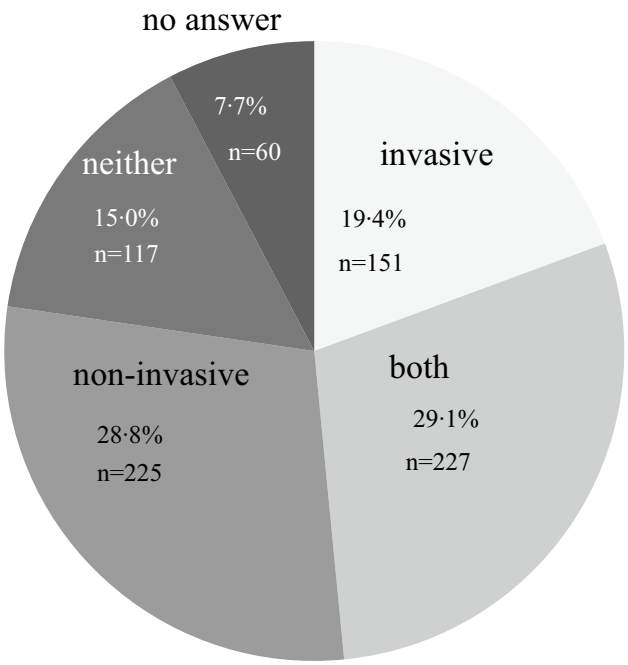

Fig. 3 Differences in expectations between non-invasive and invasive brain–machine interfaces (BMIs). Regarding communication support, movement support, and support for environmental control, the Mann–Whitney–Wilcoxon test was used to compare the expectations for each item between non-invasive and invasive BMIs. The percentage indicates the proportion of participants who selected each of the four choices for the questions for those interested in non-invasive and/or invasive BMIs. Participants interested in both types of BMIs overlapped in each group. Percentages < 1·0 are not indicated. Non-responders were excluded from the analysis

Discussion

This was the first nationwide, large-scale questionnaire survey of patients with ALS regarding BMIs. We found that nearly all participants expected communication support from BMIs. Participants without tracheostomy expected a wide range of motor support from BMIs. Nearly, 80% of participants were interested in BMIs. In this section, we will discuss the present status of patients with ALS as well as their interests in and expectations from BMIs.

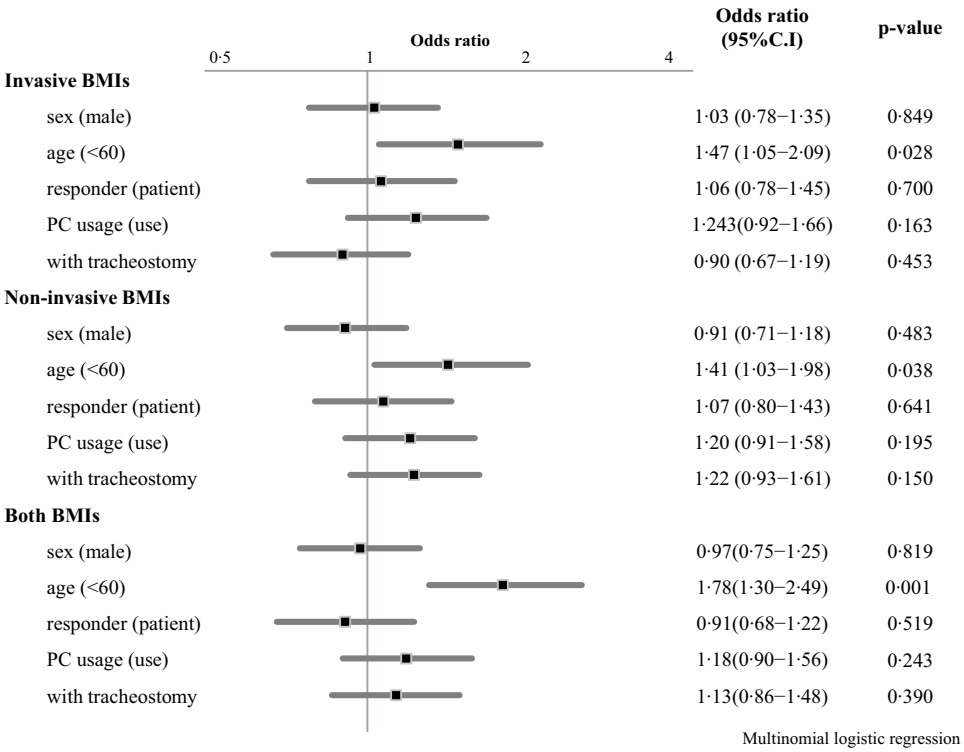

Fig. 4 Factors affecting interest in brain–machine interfaces (BMIs). Odds ratios of possible factors affecting interest in invasive BMIs only, non-invasive BMIs only, and both BMIs are indicated. The scores from the 624 participants who completely answered all of the questions [interests in BMIs, sex, age, responder type, PC usage, and simplified revised Amyotrophic Lateral Sclerosis Functional Rating Scale (ALSFRS-R)] are presented. Multinomial logistic regression was used to evaluate odds ratios. Squares indicate odds ratios, and bars indicate 95% confidence intervals

Study population

The respondent population in the present study accounted for 9% of all patients with ALS in Japan. In addition, the proportion of participants with TPPV was consistent with those of previous large-scale surveys of patients with ALS in Japan [11, 12]. These findings indicate that the present study population is both sufficiently large for reliable statistical analyses and reflective of the whole ALS population in Japan. Because BMI technology may support severely affected patients, their comments are indispensable. In this aim, the high proportion of patients with tracheostomies in this study is appropriate for investigating expectations from BMI. Because the rate of TPPV use among patients with ALS in Japan is considerably higher than that among patients in North America and the EU (1.5–4%) [18–20], there are much more severely affected patients with ALS in Japan than in other countries.

The recommendation regarding transition from NIPPV to TPPV is described in Practical Guideline for Amyotrophic Lateral Sclerosis (ALS), 2013. The guideline describes the timing of transition from NIPPV to TPPV as follows: (1) when impaired airway clearance occurs resulting from bulbar paralysis or (2) when the patient is determined to use TPPV. Since long-term care insurance was implemented in 2000, social insurance system has been fundamentally reformed in Japan. This may, in some respects, have helped to increase the use of TPPV. At present, the cost of tracheostomy ventilation and the following caregiving support is fully covered by the public medical or health insurances, which allows the patients to use long-term ventilation for only ¥1000 (around $10) per month and receive caregiving support without any cost [36]. This public medical support may help nearly 30% of patients with ALS in Japan to undergo TPPV.

Therefore, this large-scale questionnaire survey on BMIs encompassing a sufficient population of severely affected patients with ALS and tracheostomies is unique and unattainable in countries other than Japan.

Present status of patients with ALS

The distribution of the participants' simplified ALSFRS-R scores also indicated that this study population included many patients with severe ALS. We found that they had many communication problems and were not satisfied with present communication devices. Furthermore, they also experienced difficulties in replacing the input methods of communication devices due to progression of the symptoms. Nevertheless, BMIs would be able to support them, even if their symptoms progress to a total LIS and they would no longer be able to control the communication devices available at present. BMIs may consistently facilitate motor function and communication support independent of the severity of the disease.

In this respect, patients with ALS would more greatly benefit if they get acquainted with use of BMIs while their illness is still relatively mild.

Expectations from BMIs

We confirmed our previous preliminary result that patients with ALS expect a wide range of support from BMIs [15]. In particular, communication is one of the most influential factors that affect the QOL of patients with ALS. The present results illustrated that almost all participants expected conversation and emergency alarms. Beukelman et al. [21] reported that 80–95% of patients with ALS were unable to meet their daily communication needs using natural speech. In particular, patients with severe ALS have difficulties in communicating. Communication support should be the primary focus of BMIs to improve the QOL of patients with severe ALS [22, 23]. The present study elucidated that present commercial assistive communication devices need to update their input format according to the progression of the illness. Difficulties in using these devices may often cause patients with ALS to cease communication. From this viewpoint, the advantage of BMIs is further clarified. Patients with ALS may directly use both communication devices and robotic arms via their own brain control independent of disease severity. Invasive BMIs are optimal from this viewpoint because the input devices, namely intracranial electrodes, are always ready for use.

The present study indicated that movement support, particularly changing body position and controlling the bed, was highly desired by the participants, particularly the ones who did not undergo tracheostomy. Patients with ALS and severe motor weakness usually request fine position adjustment of their extremities to minimize uncomfortable sensations. Their caregivers have to spend time and effort to satisfy them. If patients can control their body position by themselves, they may be free from uncomfortable disease-related sensations, such as numbness, and their caregivers may be free from the heavy burden of postural changes. Thus, it is important to support movement function including postural changes using BMIs.

Interest in BMIs

We revealed that younger participants were more interested in both invasive and non-invasive BMIs, and frequent PC users tended to be interested in both types of BMIs (Fig. 4). Conversely, older participants or non-PC users may experience difficulties in mastering such new technologies. Silvoni et al. [24, 25] identified a negative correlation between age and the BMI skill in patients with ALS. Therefore, it may be indispensable to develop BMI devices that can easily be used even by older patients and non-PC users. Participants without tracheostomy did not display a significant difference in BMI interest regarding their invasiveness, although noninvasive BMIs will likely be preferred. Considering that movement support was more strongly expected by participants who did not undergo tracheostomy, their request for high-performance movement support may be crucial, explaining why they did not exhibit a clear negative assessment for invasiveness. Invasive BMIs should provide wide-ranging, high-performance support to offset the impact of their invasiveness.

Potential of BMIs for patients with ALS

Patients with ALS hesitate to undergo TPPV in many countries, including Japan [18, 26]. The reasons for this hesitation are incurability of the disease, loneliness caused by social isolation [27], low QOL, perception of being a burden to caregivers, and exhaustion [28, 29]. The high frequency of suicides soon after ALS diagnosis confirms the despair experienced by these patients [30]. On the contrary, Rousseau et al. reported that TPPV prolongs the lifespan of patients with ALS without affecting their QOL [31]. They also reported that significant number of patients in a LIS replied that they maintain a good QOL. Moss et al. reported that many patients in a LIS were satisfied with having chosen home ventilation and would choose it again [32]. It appears that their QOL was unrelated to their physical state despite their extreme motor and communication impairment [33]. Irrespective of the physical devastation and mental distress experienced by patients in a LIS during the acute stage of the condition, optimal life-sustaining care and revalidation of the value of living with severe motor and communication impairment can have major long-term benefits [34]. These findings imply that mental QOL remains unaffected in patients with severe ALS, although their physical QOL is extremely low [35]. However, we must remember that these positive patients comprise an exceptional minority that chose mechanical ventilation and that a large majority of patients with ALS are not able to overcome the acute stage of the disease and refuse mechanical ventilation.

The results from this study were obtained only from Japanese patients and their caregivers. However, our results are applicable not only to Japan but also worldwide. BMI technology might help patients with motor neuron disease to use communication devices and nursing equipment by themselves and lighten the caregivers' burden. We believe that BMI technology has a universal potential for changing the situation for patients with motor neuron disease, who find it too hard to choose to live, and for their caregivers, who find it difficult to support them. Actually, a fully implantable BMI device enabled independent communication with the use of typing software in a locked-in patient with ALS [9]. The support of BMIs may make it possible for patients with ALS to work and have a social life [6]. If patients are informed that BMIs can help preserve their physical QOL even after their disease progressed, they may

be not pessimistic and may be willing to live under invasive mechanical ventilation.

Limitations of this study also need to be acknowledged. Cognitive impairment, behavioral symptoms, and capacity may affect the utility of BMIs. In fact, cognitive abnormalities were more frequent in elderly patients with ALS with a disease onset age of > 65 years [37]. However, in this study, we did not design the questionnaire to identify cognitive impairment, behavioral symptoms, and capacity [12].

Our nationwide survey revealed the cruel present state experienced by patients with ALS and their eager expectations from BMIs. It is important to develop BMIs that meet patients' needs based on the results of the present survey. Implementation of BMIs that meet the expectations of patients with ALS may help to alleviate the extreme stress associated with the illness and improve patients' physical and mental QOL. If this is achieved, ALS may be transformed into a disease with a much less severe burden on patients.

Conflicts of interest

We declare that we have no conflicts of interest.

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Author contributions MH designed and mainly supervised the present study. TY, HM and HK also supervised the present study. MH, TY, YK, JS and OS designed the questionnaire. YK analyzed the data, supervised by TS regarding statistical analyses. YK, XH, MH and MS wrote the manuscript, figures, tables and supplementary materials.

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