Understanding the Psychological Well-being of Patients with Locked-in Syndrome: A Scoping Review

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Abstract

Locked-in syndrome (LiS) is a neurological disorder caused by lesions affecting the ventral pons and midbrain and is characterized by loss of physical function, but with perceived consciousness intact. Despite severe limited function, previous studies have shown the quality of life (QoL) of patients to be more positive than naturally assumed by caregivers and relatives. The present review aims to synthesize the broad scientific literature focused on the psychological well-being of LiS patients.

A scoping review was performed to synthesize the available evidence on the psychological well-being of LiS patients. Eligible studies included those that targeted individuals with LiS as the study population, evaluated psychological well-being and explored the factors related to it. We extracted study population details, type of QoL methods, method of communication, and primary findings from the studies. We summarized the findings categorized into health-related QoL (HRQoL), global QoL, and other tools for assessing psychological status.

Across the 13 eligible studies, we generally observed that patients with LiS had reasonable or similar psychological well-being as the standard based on HRQoL and global QoL assessment. Caregivers and healthcare professionals seem to rate the psychological QoL of LiS patients lower than patients themselves. Studies showed evidence that longer duration of LiS to be factor that positively affects QoL, and augmentative and alternative communication tools and recovery of speech production showed positive effects as well. Studies reported a range of 27% to 68% of patients experiencing thoughts of suicide and euthanasia.

The evidence generally shows that LiS patients had reasonable psychological well-being. There appears to be differences between patients' assessed well-being and the negative perceptions by caregivers. Response shift and adaptation to disease by patients are considered potential reasons. A sufficient moratorium period and provision of information to support patients' QoL and appropriate decision-making seems necessary.

I. Introduction

Locked-in syndrome (LiS) is a rare neurological disorder caused by lesions affecting the ventral pons and midbrain. Injuries to the ventral pons, often due to stroke (ischemic and hemorrhage) are the most common causes of LiS. Additional conditions that can cause LiS include infection in certain portions of the brain, tumors, loss of the protective insulation (myelin) that surrounds nerve cells (myelinolysis), inflammation of the nerves (polymyositis), and certain disorders such as amyotrophic lateral sclerosis (ALS) 1. LiS is characterized by patients having limited motor function (except for vertical eye movement and blinking), but still having intention or perceived consciousness with five senses and the ability of thought intact. As a result, independence and communication are severely impaired. It is differentiated from coma, consciousness disorder and vegetative state, which manifest impaired consciousness, without awareness of the self and surroundings and with no voluntary motor movements [2].

The classical form of LiS is defined as quadriplegia and anarthria with the preservation of the ability to perform vertical eye movements, blinking, and maintaining a normal level of consciousness. The incomplete form is similar to the classical form, but with limited voluntary motor functions and movement. The total form is complete immobility and loss of function including eye movement, but with consciousness intact. In the classical and incomplete forms, consciousness is often evaluated by blink-response or eye movement-response to questions [3]. Reported mortality rates for LiS vary by study and etiology; there is high risk of mortality in acute settings, but improved medical care approaches have improved long-term outcomes. Patients with medical stability of 3 years from onset showed a 10-year survival rate of 83% [4]. While the overall prevalence of LiS is largely unknown with variation by country, Kohnen et al. reported the prevalence of classic LiS in a Dutch nursing home setting to be 0.7 per 10,000 and suggested that this may be a low figure influenced by the Dutch provision of home care or end-of-life decisions (e.g. euthanasia, withholding or withdrawing medical interventions [5]. Furthermore, this study brings to light the vitally important ethical issues and fundamental questions, such as euthanasia and end of life considerations while in LiS. Although there are no available data regarding the prevalence of LiS in Japan, the same ethical issues

apply this country as well. Furukawa et al. reported that ALS patients in Japan have a higher rate of invasive ventilation (IV) use than western countries (29.30% vs 1.5-3.2%) [6]. Considering the disease prognosis, ALS patients with IV are usually at a risk of LiS, and it may be common to be living with fear of dying [7]. In Japan, this situation is likely more common than western countries among ALS patients. However, the discussion of end of life care, including legislation, is still insufficient at the national level.

Contrary to the known limits in physical function, previous studies have shown that the quality of life (QoL) of LiS patients may not be as poor as initially perceived by caregivers [8]. However, most research has been based on small sample sizes due to the rarity of the condition, and studies have varied in the measures and approach used for QoL assessment as well as the etiology of LiS targeted for examination. In a recent systematic review on the prognosis and management of LiS patients, Halan et al. described that LiS patients had poor quality of life, but noted this to be due to motor function disability which may be separate from depressive and psychiatric aliments of LiS [9]. Given the lack of cumulative knowledge on the psychological well-being of LiS patients, there is need to summarize what is known based on current evidence from the scientific literature, including an understanding of the types of psychological and QoL instruments and measures used across LiS patients of varying etiology.

In this study, we performed a scoping review with an objective to understand the available evidence on the psychological well-being of LiS patients. We expect that this review will help to identify the gaps in knowledge and inform needed areas for further research and development. This scoping review may serve as a precursor to a more targeted systematic review in the future and offer caregivers and relatives a more accurate perception of the LiS state.

2. Methods

A scoping review was performed to synthesize the available evidence from a broad perspective on the psychological well-being of LiS patients. We followed the PRISMA SCR (Preferred Reporting Items for

Systematic Reviews and Meta-Analyses extension for scoping review) which provides guidance on the methodological process for scoping reviews. Considering the small sample size of LiS cases across the specific studies and the lack of established measures for evaluating the QoL of LiS, a scoping review was considered a reasonable approach to achieving study goals.

Protocol and registration

We developed a protocol in line with the methodological framework by Arksey and O'Malley, which was later revised by Levac et al. [10]. The protocol is available through UMIN-CTR (University hospital Medical Information Network-Clinical Trial Registry, Study ID: UMIN000047630).

Eligibility Criteria

The search considered original research articles both qualitative and quantitative in design that included human subjects, and written in English. Reviews, expert opinions, and policy documents were excluded. Articles with the following characteristics were included: 1) patients with LiS targeted as the study population, and 2) evaluated psychological well-being of patients with LiS and explored the elements influencing it such as LiS etiology.

Information sources and search strategy

We searched the following databases (as of May 27, 2022): MEDLINE [PubMed], Cochrane Library and Embase related to the psychological well-being of LiS published within the last 30 years. Search terms [Mesh term] included ("Locked-in syndrome" OR "Locked-in state") AND ("Quality of life" OR "well-being" OR "psychological") in the title or abstract.

Study Selection

The references extracted from the databases were imported into an article screening tool (Rayyan) which can detect duplicated references. Two investigators (HY and NM) reviewed the titles and abstracts independently

examining the references based on eligibility criteria. If a study appeared to meet the inclusion but there was doubt regarding the eligibility of the article, full text review was conducted for each article by both investigators. If disagreement could not be resolved, a third reviewer (KU) was included.

Data Items

Data for extraction included publication details, study population details, type of QoL methods, and method of communication. Publication details included authors, year, country of study and study design. Participant's details include number of participants, mean age, gender, etiology of LiS, average time from onset, residential environment and physical status. Communication methods included whether patients expressed intention by eye-blinking, use of augmentative and alternative communication (AAC) systems, face movement, residual verbal approaches, or letter board. The type of person who interacted with patients to completes the QoL assessment in each study (investigator, caregiver or healthcare professional, etc.) was also noted.

Evaluation approach

We divide the type of QoL and psychological well-being tool into three groups, including health-related QoL (HRQoL) designed for the general population, global QoL (subjective QoL) developed for intractable diseases, and other tools for assessing psychological status. In addition, we categorized some study results into "reasonable one" for LiS patients (reasonable) and "negative" for LiS patients (negative) in the case that each psychological well-being tool had the standard/ reference score or the study compared the psychological well-being status between LiS patients and control group. If each psychological well-being tool in the study showed better or near outcome in LiS patients compared to its standard score or control, we defined the result as "reasonable". In contrast, when the study tool showed worse result in LiS group, we stated the result as "negative". The standard/ reference score of each psychological well-being tool is shown in Table 3. We evaluated the articles based on various aspects, such as a type of instruments used, patient characteristics, disease duration, country of origin, religion and other exploratory factors.

3. Results

A total of 181 records were detected from our search strategy. The details of the screening process at each step are shown in Figure 1. In total, 13 studies met the eligibility criteria, and the country of origin of the studies included the United States, France, Italy, Poland, Belgium, Sweden, Germany, and the United Kingdom. Three were longitudinal studies, nine were cross-sectional in design, and one was a case study (Table 1). In line with the epidemiology of the LiS population, eight studies mainly include LiS patients with vascular etiology mostly due to stroke, two studies targeted LiS caused by ALS which is often a gradual process that takes several years, one study included patients with LiS (vascular or tumoral etiology) and ALS without LiS. Two studies had no data about the etiology of LiS. While the disease duration varied across studies, most examined stable LiS patients in which the disease period was over 2 years, except for one study [11].

Across the studies, 17 different instruments for QoL and psychological well-being assessment were utilized. Among them, 15 were established or validated tools with standard score or comparable score based on the general population, and 2 were original questionnaires created for the studies (Table 2). The most common tool used was the SF-36 (RAND-36) [12], adopted by six studies. The Anamnestic Comparative Self Assessment (ACSA) [13] was used in four studies. Each of the following instruments were used in two studies; Schedule for the Evaluation of Individual Quality of Life-Direct Weighting (SEIQoL-DW) [14], McGIL QOL [15], Beck Depression Inventory (BDI-II) [16], and ALS Depression Inventory-12 items (ADI-12) [17]. Within 16 established instruments, 3 measured HRQoL (SF-36, WHO-5 [18], EQ-5D [19]), and 3 measured global QoL, (ACSA, SEIQoL-DW, McGIL QOL). Nine instruments were for measuring psychological status for depression, anxiety, autonomy, coping and alexithymia. The last instrument was a questionnaire for assessing end-of-life issues (Table 3). Overall, most studies showed reasonable results regarding psychological well-being and QoL across the different etiologies of LiS.

Findings from HRQoL designed for general population

Seven studies included an HRQoL assessment. SF-36 (RAND-36) was used in six studies [11, 20-24] and each WHO-5 and EQ-5D was in one study, respectively [2522]. Two studies with SF-36 provided reasonable results, in which LiS patient's group showed nearly score to control or norm group. Other four studies with SF-36 did not set the control or reference group, however, two of them showed the score of Mental Health domain with 75 and 90, respectively [22,7] and one study provided the mean SF-36 score with 75.1[23]. These scores are corresponding to the general population in previous report from Wales 26. One with WHO-5 also presented reasonable results in LiS patients with the mean score of 63.6 (reference score of WHO-5 is 60.0). EQ-5D in one study showed negative values in which three of four participants reported values of less than 0 (score under 0 in EQ-5D is described as indicating a condition worse than death). However, authors interpreted this result as physical functioning having a significant impact on EQ-5D results.

Findings from global QoL designed for intractable diseases (subjective QoL)

Seven studies utilized the global QoL for intractable diseases [20,23,25, 27-30] and showed reasonable results with the exception of one study [30]. Among the four studies using the ACSA, three showed reasonable outcomes presenting mean values of greater than 0 or a majority of participants with a value of greater than 0 [27-29]. One study recruited a diverse series of patients including LiS and reported LiS as a major subgroup who reported poor outcomes based on the ACSA [30]. Considering that the ACSA incorporates features of a highly individualized biographical scale, ACSA might not be a suitable tool for relative comparisons.

Findings from questionnaires for psychological status

Among nine studies that included this type of assessment, seven administered assessment tools for depression, including ADI-12, BDI, the Hospital Anxiety and depression scale (HADS) [31], and an original questionnaire. Among three studies using the BDI, two indicated borderline clinical depression with scores

of 17 or greater or moderate depression in LiS patients [11,23], and one study reported more frequent depressive symptoms in the LiS group than healthy controls [20]. Whereas a study using HADS showed almost no symptom of depression with score of 1. In two studies, ADI-12, which was developed for ALS patients, also showed normal state in LiS patients with mean scores of 25 [27] and 19.7 [25]. One study asked about the presence of depression and showed that 13% answered being depressed [16].

Regarding anxiety, State Trait Anxiety Inventory (STAI-Y) [32], Hamilton Anxiety Rating Scale (HAM-A) [33] and HADS was used in each one study and two used original questionnaires. STAI-Y presented clinically significant anxiety symptoms in LiS patients with each of the basal (trait) and reactive (state) scores showing to be greater than 50 [23]. HAM-A showed mild-moderate anxiety in LiS patients with mean score of 21 at baseline, but after 3 months, indicated normal with mean score of 16 [11]. HADS showed a normal status with a score of 5 [24]. One study asked about the anxiety status (none, moderate, extreme) and showed 54% of patients with moderate anxiety and 13% with extreme [29]. Another study inquired about the presence of anxiety/depression and reported 55% of patients with anxiety and/or mood disorders at baseline [28].

One study examined participation/ autonomy by IPA-E (Impact on Participation and Autonomy) [34]. Results showed a reasonable score compared to the reference data [22]. Coping status was measured by motor neuron disease coping scale [35] in one study and showed that information-seeking increased with time since diagnosis only [27]. Alexithymia was assessed by The Toronto Alexithymia Scale (TAS) [36] in one, and it showed possible alexithymia with scores of 56.9 and 60.3 [23].

Perception of psychological well-being between patients and caregiver/ next of kin

Two studies showed similar results in which caregivers or next of kin (NOK) tended to rate the patients QoL lower and overestimated patient's depression, but differences were not significant [25, 27]. These results were in line with previous reports for another fatal disorder, cancer patients and caregivers [37]. Researchers

suggested that the differences may be due to inconsistencies between patients and next of kin in terms of important features of life that are of value and it appeared to reflect the successful adaption (adaptation) to the disease by the patients, but not by the NOK [25].

End-of-life issues

Five studies assessed the end-of-life issues [4,21,27-29]. One study used statements on wish for hastened death (SAHD) [38] and participants presented a middle level wish for hastened death with mean score of 4.5 [27]. Across the remaining four studies, participants were asked about suicidal thoughts and euthanasia and studies reported a range of 27% to 68% having these types of thoughts (Table 4). Patients in these five studies all had stable LiS with over 6 years of disease duration.

Influential factors on psychological well-being

Seven studies examined factors associated with QoL or well-being. Disease duration was a factor assessed most commonly. Among four studies, half found longer duration to be a factor positively affecting QoL [25,29], while the other two did not find a relationship [27, 28]. Regarding the influence of communication methods, AAC tools and recovery of speech production showed positive effects [11,29], whereas Yes/ No code use showed to negatively impact QoL [29]. Thus, the communication modalities with high flexibility appeared to be positively associated with patient's well-being. Among the studies that performed an assessment, most found that physical function had no relation to QoL, rather one study showed that disease severity was positively correlated with QoL. In addition, Kuzna et al. reported that LiS patients in ALS with no residual physical function (ALSFRS-R = 0) showed positive QoL and no clinically significant depression [25, 27]. Experiencing anxiety and suicidal thoughts was found to be negatively associated with QoL [28, 29].

Global QoL and HRQoL results did not show marked patterns regarding the country of the study. However, for the depression scales, there appeared to be a tendency for negative results in studies from southwestern

Europe, France and Italy [11, 20, 23], and reasonable or normal results in studies from central Europe, Poland and Germany [25, 27]. However, different depression scales were used and the results may be due to the type of depression instruments rather than geographic character. Studies with reasonable results used ADI-12, which is a depression scale developed for ALS and patients with limited physical function, whereas study with negative results for depression used BDI. BDI has the possibility to overvalue depression in patients with physical function loss because the scores of BDI are susceptible to physical disability [39].

4. Discussion

The present study is, to our knowledge, the first review with the aim to synthesize the evidence regarding the psychological well-being of patients with LiS. Across the 13 eligible articles, we generally observe that patients with LiS had reasonable or similar psychological well-being as the standard regardless of etiology, socio-demography and physical disability level. These results appear different from the previous systematic review by Halan et al., which is likely due to this current study focusing on psychological well-being. Halan et al explained that poor quality of life of LiS patients was primarily caused by motor function disability which may be different from psychological issues [9].

Caregivers and healthcare professionals seem to rate the psychological QoL of LiS patients lower than patients themselves. This tendency is consistent with other fatal disorders [37, 40]. Linse et al. explained that this may reflect the successful adaptation of the patients to the disease and that a “response shift” may have occurred in patients with LiS [25]. Psychological adaptation has also been described by others [27-29,41] and is a well-known phenomenon in diseases, such as ALS or advanced-stage cancer [37,40, 42, 43].

Potential driver for psychological well-being of LiS patients

Sprangers et al. defined the response shift as involving, 1) recalibration for a new scale in measuring one’s own state of quality, 2) reprioritization that represents change in the priority of values influencing one’s own QoL, and 3) reconceptualization consisting of a reconstruction of one’s own concept; for example, patients

place greater weight on inner and spiritual value after serious illness [44]. We can consider these shifts as an important process for adaptation among LiS patients influencing the QOL of patients in a positive manner. Global QoL (subjective QoL) may be influenced more sharply by the response shift compared to HRQoL, such as EQ-5D.

Considering the importance of adaptation for the well-being of LiS patients, it seems reasonable to observe that disease duration was associated with successful psychological outcome. Studies showed positive correlation between disease duration and psychological well-being. Among the studies in this review, three were longitudinal studies with a follow up period of 6 years, 11 years and 3 months [4,11,28]. The study with the 6-year follow-up showed no significant difference of ACSA score within the period, however the prevalence of anxiety and mood disorder declined from 55% to 31%. The study with a 3-month follow-up showed meaningful improvement of SF-36 score, depression and anxiety, but we need to consider that acquisition of communication ability with the AAC tool in this study period may have impacted the QoL status. The study with 11-year follow-up did not provide a comparison of well-being across the observation period. Considering the duration from time of onset, all seven studies including patients with disease duration of greater than 5 years showed reasonable results or similar scores to the standard population regarding QoL or psychological well-being 4,21,22,25, 27-29]. In contrast, two studies with disease duration of less than 3 years showed negative aspects among the psychological domains [11, 23]. In the one case study, the patient with 2-year disease duration reported a reasonable QoL and reported better general health than a year ago [24].

As another description of the effect of adaptation, Kuzma et al. reported that patients with good psychosocial adaptation were also the ones who were well-informed [27]. Interestingly, well-informed and transparent information were also identified as unfulfilled needs of LiS patients in other studies [21, 22]. Transparent information includes the precise pathophysiology of LiS, its prognosis, latest technologies including advanced communication devices, social support system, and proper care. There is sentiment that this information should be given to the patients with respect, and caregivers (and public) would benefit by

obtaining an understanding similar to that of the patients [22].

Implications

Given that disease duration and being well-informed are associated with adaptation and well-being of patients, end-of-life decision in the early phase of LiS should be provided discretely. Regarding the end-of-life issue and thoughts of suicide and euthanasia in the present review, LiS patients presented a middle level wish for hastened death, while these ideas tended to have decreased over time. Bruno et al. also suggested that a moratorium should be proposed for patients with suicidal thoughts in the acute setting [29]. At the same time, the patient's perception of being a burden to caregivers was identified as a determinant to wishing for a hastened death, as well as for depression, anxiety and poor QoL [45]. Thus, when we consider the end-of-life issue for LiS patients, it may be meaningful to also consider issues of caregiver burden, and not only support focused on the patients. Financial aid and social support, such as respite care (short term assistance serving rest and relief for caregivers) may be a vitally important resource for both patients and caregivers [46].

Communication methods with high flexibility are also important to improve QoL in patients with LiS. Studies indicate that the AAC tool and Eye-Tracking Computer System (ETCS) could help to improve QoL of patients [11,25]. However, when the possibility is available, recovery of speech product is a better way to communicate naturally and may be a positive factor for the well-being of patients. Most studies of LiS patients with vascular etiology in this review noted the importance of multidisciplinary rehabilitation because it might improve the prognosis and has the possibility to make LiS patients regain voluntary head control, finger movement, and sometimes partial speech production. A rehabilitation plan and strategy for LiS should be developed in an individualized fashion considering disease phase due to the variation in LiS pathophysiology.

In the clinical setting, transparent information should be provided to both LiS patients and caregivers, and

healthcare professionals and caregivers should also understand the actual psychological QoL of patients without pre-conceptions. A sufficient moratorium period should be secured for patients to support decision-making. Previous studies have shown that low health literacy is associated with low QoL [47]. Selection of an appropriate QoL instrument is also important. HRQoL and general tools for assessing depression could underestimate the QoL state and overestimate the depression in patients with LiS. There is a need to develop suitable instruments for assessing psychological well-being specific for LiS patients in order to understand their mental health in an accurate way.

For the policy and public health setting, it is necessary to provide broad social support mechanisms including financial, medical, communication devices and a system of social support to both patients and caregivers to help secure their dignity, autonomy and wellness. Hofman et al reported on the connections between the improvement of social support and an increase in the QoL of lung cancer patients, another fatal disease [48].

Particularly, in Japan, there is little discussion about end of life issues. To allow a fair decision-making process with dignity for patients, social support including education about end of life issues at an appropriate communication level well in advance is needed. The opportunity for education in various settings could provide a better understanding of the LiS situation, not only for patients but also caregivers, relatives and society. Multi-disciplinary approaches for legislation pertaining to euthanasia at the national level should also be considered.

Limitations

There are limitations to acknowledge regarding this scoping review. Some included studies noted that patients who could not participate in the study might have had poor QoL. It is possible that excluded subjects from the studies may be those with limited interactions with society and severe physical and mental situations. Thus, this review may not be appropriately capturing the circumstances of these subset of patients. From the present review, we did not observe different tendencies for psychological QoL across LiS

of different etiologies. However, the time course from underlying disease onset to complete LiS varies depending on etiology. For example, LiS caused by ALS develops gradually, while LiS with a vascular etiology is sudden. Thus, coping and adaptation processes of patients may be different. It can be adapting to the rehabilitation strategy. The rehabilitation for sudden onset LiS sometimes aims to regain motor function even if it is only limited recovery, while rehabilitation for LiS in ALS or other fatal neurodegenerative diseases tends to maintain residual functionality for longer periods. Thus, further research for developing the care and coping strategy for LiS by etiology and type of LiS will be a significant contribution.

5. Conclusion

In reviewing the 13 studies that met eligible criteria, we found that patients with LiS generally had reasonable or similar psychological well-being as the standard population. Caregivers' perception and the patients' assessed QoL were observed to be different in some studies. Response shift and adaptation to disease by patients (not by caregivers) are considered as a potential reason for this gap. Disease duration and being well-informed with transparency may influence this process. Given these observations, it seems important to provide a sufficient moratorium period and provide appropriate information including social support and care options for patients to aid the decision-making process.

Declarations

Conflicts of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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Figure 1. PRISMA Flow: Articles selection process

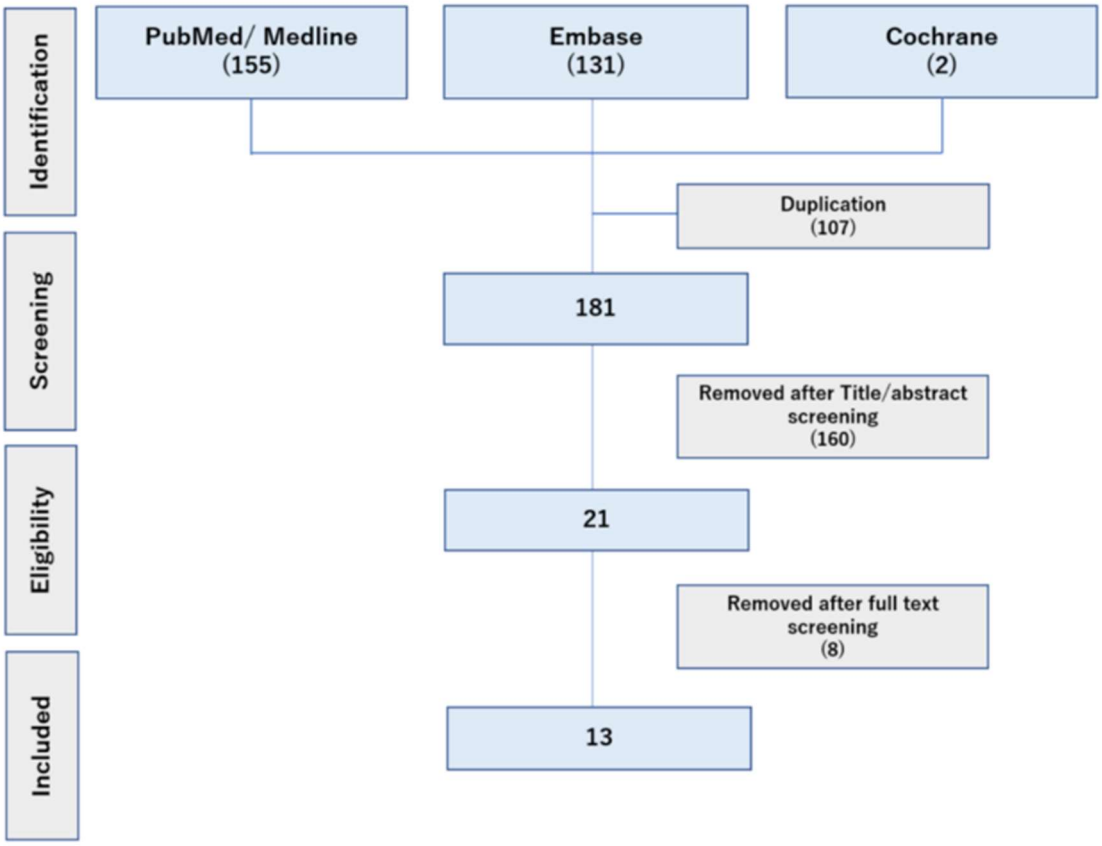

Table 1: Basic infromation of 13 studies included in the scoping review

ID	Author, year of publication	Design	Country	Objectives	Sample size (male)	Methods of psychological QOL	Religious yes/no	end-of-life issue
1	Kuzma-Kozakiewicz M et al, 2019	Cross-sectional	Poland	Well-being and end-of-life preferences	19 (13)	ACSA[1], SEIQoL-DW[2], ADI-12[3], SAHD[4], Motor Neuron Disease Coping Scale	-	○
2	M-C Rousseau et al, 2015	Longitudinal	France	The course of the QoL over a 6y and determine the potential contribution	67 (41) at 2007 39 (24) at 2013	ACSA, questionanaire for psychological status	46/19	○
3	M-C Rousseau et al, 2013	Cross-sectional	France	Compared QoL of LIS with healthy controls	No data	MCGIL, SF-36, BDI-II[5],TAS[6]	-	-
4	L Snoeys et al, 2013	Cross-sectional	Belgium	Explore the situation of chronic LIS incl. QoL	8 (4)	SF-36, specific questions related to aspects relevant to changes due to LIS	-	○
5	K Svernling et al, 2018	Cross-sectional	Sweden	Explore LiS in Sweden characteristics inc. QoL	10 (7)	RAND-36, IPA-E[7] and EQ-5D[8]	-	-
6	Linse K et al , 2017	Cross-sectional	Germany	Assess QoL and psychological well-being of LIS	11 (6)	ADI-12, WHO-5, SEIQoL-DW	-	-
7	MA Bruno et al, 2011	Cross-sectional	France	Self-assessed QoL in chronic LIS	65 (43)	ACSA	40/17	○
8	M-C Rousseau ea al, 2011	Cross-sectional	France	Compare QoL of ALS and LIS w/ and w/o Invasive Ventilation	34 (22)	McGILL, SF-36, BDI-II, TAS, STAI-Y[9]	-	-
9	J E Doble et al, 2003	Longitudinal	USA	Long-term outcome of patients with LIS	29 (19)	original questionnaire for satisfaction with life and end of life	-	○
10	MC Nizzi et al, 2011	Cross-sectional	France	(A) global evaluation of identity, (B) body representation (C) meaning in life	44 (30)	Original three parts questionnaire	-	-
11	Bernheim, J.L et al, 2019	Cross-sectional	Belgium	Effectiveness of ACSA as QoL tool on various patients	2500 *diverse patients not only LIS	ACSA	-	-
12	F Corallo et al, 2017	Longitudinal	Italy	The impact of the AAC on the QoL of LIS and caregivers	15 (9)	SF-36, HAM-A[10], BDI-II	-	-
13	B A Wilson et al, 2011	Case report	UK	Neuropsychological assessment of LIS	1 (0)	HADS[11], SF-36	-	-

Abbreviations

1: ACSA -Anamnestic Comparative Self Assessment, 2: SEIQoL-DW -Schedule for the Evaluation of Individual Quality of Life-Direct Weighting, 3: ADI-12 -ALS Depression Inventory–12

4: SAHD -Statements on wish for Hastened Death, 5: BDI-II -Beck Depression Inventory, 6: TAS- Tront Alexithymia Scale, 7: IPA-E -Impact on Participation and Autonomy,

8: EQ-5D -Euro QOL 5 Dimensions, 9: STAI-Y -State Trait Anxiety Inventory, 10: HAM-A -Hamilton Anxiety Rating Scale, 11: HADS -Hoapital Anxiety and Depression,

Table 2. Characteristics of participants included in each study

ID	Author, year of publication	Mean age *Median	Etiology of LiS	Mean time from onset *Median time	Physical status PEG[1]/IV[2]	Caregiver/ environment	Communication style eye-blink/eye-chat/etc,
1	Kuzma-Kozakiewicz M et al, 2019	59	19: ALS	92m	17: IV** 18: PEG	16: Partner 2: Children 1: Professional	9: Eye-tracking, 6: Eye-blink 3: Combination 1: Residual verval
2	M-C Rousseau et al, 2015	*47 at 2007 *51 at 2013	51: Stroke , 8: Traumatic , 3: Others at 2007 31: Stroke , 4: Traumatic , 3: Others at 2013	*8y at 2007 *14y at 2013	22: IV, 20:PEG at 2007 patients with IV and PEG decline at 2013	20: Institutional, 26: home at 2007 6: Institutional, 27: Home at 2013	77%: Yes/ No cord 58%: Computer communication device at 2007
3	M-C Rousseau et al, 2013	No data	1: Trauma Others: Vascular etiologies	No data	No data	No data	No data
4	L Snoeys et al, 2013	41.1	7: Stroke 1: Trauma	6y8m	0: IV 6: PEG	8: Home	1: verbal, 5: Partly verbal 4: Set of gestures, 7: Head & facial movement 6: Eye codification
5	K Svernling et al, 2018	*49	7: Ischemic stroke 3: Hemorragic	*5.9y	IV: no data 2: PEG	2: Nursing home 1: Apartment with society support 4: Independent, 3: No data	1: Oral communication Others: letter boards/ eye-tracking computer device or blink.
6	Linse K et al , 2017	54.7	11: ALS	6.5y (from ALS onset)	82%: IV 82%: PEG	10: Home w/ 24h nursing care	11: Eye tracking
7	MA Bruno et al, 2011	49	Most is acute anterior pontine leison	8y	No data	42: Home 23: Institution	Only data about speech production, None: 45% Words: 19%, Sentence: 36%
8	M-C Rousseau ea al, 2011	56.7	27: ALS, 7: LIS, (6: vascular, 1:tumoral)	*29m	12: IV 19: PEG	34: Hospital	No data
9	J E Doble et al, 2003	33.6	48%: Vascular 34%: trauma 10: hypotention, 2: Others	>11y at study end	7: IV, 19: PEG at initiation 2: IV, 6: PEG at 11y after	8: Live w/ family, 3: Care facility 1: State run school 1: Hospital w/ nursing	4: Computer use, 3:Letter board 3: Facial movement, 2: Limb movement 1: Vocalizations
10	MC Nizzi et al, 2011	53	No data	No data	No data	All at home	Eye-blink
11	Bernheim, J.L et al, 2019	no data	No data	No data	No data	No data	No data
12	F Corallo et al, 2017	48.65	15: hemorrhage	1m after onset at T0 3month after T0 at T1	No data	15: Hospital at T0 8: Hospital, 7: Own home at T1	15: The AAC tool[3]
13	B A Wilson et al, 2011	29	Basilar artery thrombosis	>2y	1: PEG	1: Hospital	1: Letter board

Abbreviation

1: PEG: Percutaneous Endoscopic Gastrostomy, 2: IV: Invasive Ventilation, 3: AAC tool: Altanative Augmentative Communication too

Table 3. The instruments used to measure quality of life and psychological status among the studies

ID	QoL/ Psychological exam	Category	No. of Study	Description	Standard or reference score
1	ACSA -Anamnestic Comparative Self Assessment	Global QoL	4	Patient is asked to judge his or her global quality of life in relation to the worst (−5 on Likert scale) and best (+5) experience in one's own life	(≥0 indicates positive QoL)
2	SEIQoL-DW -Schedule for the Evaluation of Individual Quality of Life-Direct Weighting	Global QoL	2	Determine their 5 most relevant fields of QoL, the share of each field for the subjective QoL, and the overall satisfaction with this field.	50(range 0%–100%; ≥50 indicates satisfactoryQoL)
3	ADI-12 -ALS Depression Inventory–12 items	Depressiveness for ALS[1] patient	2	Addresses the patient's affective state. Response options are fully agree (1) to fully disagree (4), adding up to scores 12–48	≤28=normal
4	SAHD -Statements on wish for Hastened Death	End-of-life	1	Patients indicated wish for hastened death with the schedule for attitudes towards hastened death with binary options (correct/wrong) to respond to 20 statements	<10=not clinically significant wish
5	Motor neuron disease coping scale	Coping status	1	22 items that can be subsumed under 6 subscales of support, positive action, independence, avoidance, information seeking, and positive thinking.	≥4=positive
6	SF-36/RAND-36* *scoring of pain and GH are different	HRQoL[2]	6	Consists of 8 items: physical functioning, role physical, bodily pain, general health, vitality, social functionung, role emotional, mental health	Reference score is different according to each region
7	BDI-II -Beck Depression Inventory	Depressiveness	2	Respond to 11 statements (0) I do not feel sad.(1) I feel sad. (2) I am sad all the time and I can't snap out of it. (3) I am so sad or unhappy that I can't stand it.	0–9: indicates normal or minimal depression 10–18: indicates mild depression 19–29: indicates moderate depression 30–63: indicates severe depression
8	IPA-E -Impact on Participation and Autonomy	Autonomy	1	Score 0 (very good) to 4 (very poor) on five domains, 39 questions: autonomy indoors, family role, autonomy outdoors, social life and relationships, work and education	Ref. mean 1.48 in social life domain Iranian stroke population, assessed 5–36 months after their stroke.
9	EQ-5D -Euro QoL 5 Dimensions	HRQoL	1	Assesses health in five dimensions:mobility, self-care, usual activities, pain/discomfort and anxiety/depression	score under 0 is described as indicating a condition worse than death
10	WHO-5	HRQoL	1	Rating on 5 items, (1) I have felt cheerful, (2) I have felt calm, (3) I have felt active and vigorous, (4) I woke up feeling fresh and rested, (5) Daily life has been filled with things interest me.	≥60 means better (totally feel them more than half of time)
11	McGill QoL	Global QoL	2	Rate 0-10 on 16 items. 1-4: physical, 5-8: psychological, 9-14: existential, 15.16: support area MQoL-EW=existential well-being, MQoL-Ps= psychological symptoms	No reference score
12	HADS -Hoapital Anxiety and Depression	Scale for depression and anxiety	1	Rate 0-4 on 7 items for each depression and anxiety	≤7=normal for each item, 8-10=boarderline, >10=abnormal
13	HAM-A -Hamilton Anxiety Rating Scale	Measure the severity of anxiety	1	Rate a scale of 0 (not present) to 4 (severe) on 14 items	14-17 indicates mild severity, 18–24 mild to moderate severity and 25–30 moderate to severe
14	TAS- Tront Alexithymia Scale	Alexithymia	2	20-item instrument that is one of the most commonly used measures of alexithymia	Equal to or less than 51 = no alexithymia, scores of 52–60: possible alexithymia, equal to or greater than 61 = alexithymia
15	STAI-Y -State Trait Anxiety Inventory	Anxiety	1	40 self-report items on a 4-point Likert scale. Measures two types of anxiety – state anxiety and trait anxiety	The cut point of 39-40 has been suggested to detect clinically significant symptoms for the S-Anxiety scale

Abbreviations

QoL=Quality of life, 1: ALS=Amyotrophic Lateral Sclerosis, 2: HRQoL=Health Related QoL

Table 4. Studies assessing end-of-life issue in participan

ID	Author, year of publication	Sample size (male)	end-of-life issue
1	Kuzma-Kozakiewicz M et al, 2019	19 (13)	Patients presented with a median wish for hastened death of 4.5 of SAHD[1] score.
2	M-C Rousseau et al, 2015	67 (41) at 2007 39 (24) at 2013	27 % had suicidal thoughts and 2 reported a wish for euthanasia at 2007 No one wishing for euthanasia and 3 reported new suicidal ideas at 2013
4	L Snoeys et al, 2013	8 (4)	Suicidal thought; 5: never, 1: did in past, 1: sometimes, 1: often, Euthanasia; 4: never, 2: in past, 2: currently
7	MA Bruno et al, 2011	65 (43)	Suicidal thought; 68%: Never, 24%: Ocacionally, 8%: Often Euthanasia; 47%: Never, 53%: Envisaged
9	J E Doble et al, 2003	29 (19)	Euthanasia/ Suicidal thought from reported resource 7: never, 6: considered in the past but not currently, 1: wish to die

Abbreviation

1: SAHD -Statements on wish for Hastened Death