Original Article

Influence of loneliness and social isolation on the diagnosis and treatment of Japanese patients with advanced lung cancer: a prospective cohort study

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Background: Social determinants of health (SDHs) are social factors that affect human health; loneliness and social isolation are core SDH factors. There is a possibility that SDHs are related to passive decision-making. However, few studies have evaluated SDHs, especially social isolation and loneliness, among lung cancer patients. This study aims to investigate the effects of social isolation and loneliness on the diagnosis and treatment of Japanese lung cancer patients.

Methods: This is a prospective cohort study that was conducted in a tertiary referral hospital in Japan (University Hospital Medical Information Network registration: UMIN000031810). The enrollment period was between April 2018 and March 2020. Patients with clinical and/or pathological diagnosis of lung cancer were enrolled in this study. Exposures were social isolation and loneliness, and main outcomes were diagnosis methods and whether the initial treatment involved active therapy or best supportive care (BSC). The confounding factors were defined as sex, age, smoking status, respiratory symptoms, weight loss, presentation with any symptoms, Eastern Cooperative Oncology Group (ECOG) performance status, tumor nodes metastasis (TNM) classification, driver gene mutations [i.e., epidermal growth factor receptor (*EGFR*), anaplastic lymphoma kinase (*ALK*)], and programmed death-ligand 1 (PD-L1) tumor proportion score.

Results: The study enrolled 264 patients who were divided into quartiles according to their loneliness scores and into two groups according to the social isolation level. Univariate analysis, complete case analysis, and multivariate analysis with multiple imputation failed to detect significant differences in diagnostic method or initial treatment strategy according to loneliness or social isolation level.

Conclusions: Physicians may not need to consider a patient's loneliness and/or social isolation when diagnosing lung cancer and selecting treatment under universal health insurance coverage. Further studies are needed to understand the influences of loneliness and social isolation on the prognosis of lung cancer patients.

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Keywords: Social determinants of health (SDHs); loneliness; social isolation; lung cancer

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Introduction

Social determinants of health (SDHs) are social and economic factors that influence human health (1). The College of Family Physicians of Canada categorizes SDHs as food insecurity, education, child development, social security, job security, unemployment, working environment, gender, sexual orientation, social exclusion, and access to health services (1). At an international conference in Rio de Janeiro in 2011, the World Health Organization emphasized SDHs as factors that could be addressed to promote health equality (2). The main focus of SDH research is on social interactions, which may involve issues with social isolation and loneliness and may influence the individual's living environment, access to services, and physical activity. Among SDH factors, upstream factors are at the macro level, such as race, nationality, and socio-economic status; loneliness and social isolation are thought to be in this category. Midstream factors are intermediate ones, such as health behaviors, education, and financial status. Downstream factors are the ones directly related to health, such as prevention, diagnosis, or treatment. Upstream factors influence midstream factors, and midstream factors influence downstream factors (3). Malcolm *et al.* (4) defined social isolation as "the objectively quantified shortfall in an individual's social relationships often measured in terms of social network size, diversity or frequency of contacts" and loneliness as "a perceived deficit between actual and desired quality or quantity of relationships".

A systematic review indicated that social isolation and loneliness were associated with higher mortality rates, regardless of whether they were linked to underlying medical conditions (5). Hyland *et al.* also reported that loneliness might be a manifestation of depressive symptoms and low quality of life (6). Social isolation also has mental and physical effects. While various studies have evaluated SDH in the general population, few studies have evaluated cancer patients (3). Previous cohort studies have indicated that living in a high deprivation area, uninsured status, and low education level were prognostic factors for lung cancer patients (7-10). However, the effects of social isolation and loneliness, as core SDH factors, remain unclear. Pezzi *et al.* reported that government insurance coverage influences decreased use of radiotherapy (8). This indicates that social interactions, which are reflected in loneliness and social isolation, may decrease pathological diagnosis or active treatment. We assume that loneliness and social isolation may influence the determination of diagnosis and treatment among cancer patients because these factors are upstream relative to economic or education SDH factors (3). Therefore, this study aimed to investigate the effects of loneliness and social isolation among Japanese patients with advanced lung cancer. First, we evaluated whether loneliness or social isolation were associated with an increased clinical diagnosis rate among lung cancer suspectable patients. Second, we evaluated whether loneliness or social isolation were associated with an increased proportion of best supportive care (BSC) as the first treatment after a confirmed lung cancer diagnosis.

Methods

Study design and setting

This prospective cohort study complied with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement (available at http://dx.doi.org/10.21037/apm-21-402). The study was performed at a Japanese tertiary referral hospital (Hyogo Prefectural Amagasaki General Medical Center) between April 2018 and March 2020. The study protocol has previously been published (11) and was approved by the Hyogo Prefectural Amagasaki General Medical Center (# 29-164). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). All patients provided written informed consent before their enrollment.

Evaluating the method for diagnosing lung cancer

The eligibility criteria for the analysis of diagnostic method were (I) a clinical suspicion of lung cancer based on computed tomography findings or other factors, (II) the

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patient was considered unsuitable for curative surgery (to avoid missing surgery-related data), (III) no treatment for lung cancer during the previous 2 months (as some cases required urgent treatment before the patient might be able to complete the questionnaire and we wanted to allow for 2 months after the start of treatment), and (IV) the patient provided written informed consent to participate in the study. The exclusion criteria were: (I) inability to complete the questionnaires (e.g., because of dementia or psychological disease) and (II) a physician's judgment that the patient was not suitable for the study.

The exposures of interest were defined as loneliness and social isolation. Loneliness was assessed using the third Japanese version of the University of California, Los Angeles (UCLA) Loneliness Scale (3–12 points) (12). To ensure that the patients could answer the questions easily, we revised the UCLA scale into a 3-question version (13). Because that tool did not have defined cut-off values, quartiles were used to categorize the participants (low to high loneliness) to help create relatively homogenous groupings. Social isolation was assessed using the Japanese version of the Lubben Social Network Scale (LSNS-6) (14). As a cut-off value for the Japanese version has not been defined, the cut-off value from the English version was used (at 12 of 30 points) (14). All patients completed the questionnaires at the time of enrollment.

The main outcome was a clinical or pathological diagnosis of lung cancer. Potential confounding factors were evaluated at enrollment, which included sex, age, smoking status, presentation with any symptoms, dementia, Eastern Cooperative Oncology Group (ECOG) performance status, and the 8th edition of the American Joint Commission on Cancer and Union for Cancer Control tumor node metastasis (TNM) classification stage (15). The presence of dementia was assessed using the Life Function Evaluation for Care Provision (16).

Evaluating the initial treatment

Patients with pathologically diagnosed lung cancer were subsequently considered to analyze the initial treatment strategy (BSC or active treatment). Patients with a clinical diagnosis were excluded from this analysis. The exposures were defined as loneliness and social isolation. The confounding factors were defined as sex, age, smoking status, respiratory symptoms, weight loss, presentation with any symptoms, ECOG performance status, TNM classification, driver gene mutations [i.e., epidermal growth factor receptor (*EGFR*), anaplastic lymphoma kinase (*ALK*), and c-ros oncogene 1 (*ROS1*)], and programmed death-ligand 1 (PD-L1) tumor proportion score.

Active therapy was defined as palliative chemotherapy or chemoradiotherapy with curative intent starting at <3 months after enrollment. Because every lung cancer patient receives BSC, regardless of active treatment status, we assigned patients who did not start active treatment within 3 months after enrollment to the BSC group, including palliative radiotherapy and complementary or alternative medicine.

Patients were judged for enrollment in the study by physicians with inclusion and exclusion criteria. At the time of enrollment, physicians handed the questionnaires with a consent form. The presence of dementia was assessed using the Life Function Evaluation for Care Provision (16). Patients submitted the paper to physicians or nurses. After enrollment, the patient received regular care. Treatment and diagnosis data were collected from the chart. When patients were referred to other hospitals, we requested their information from the hospital.

Statistical analysis

The protocol planned to recruit 300 patients, although recruitment was terminated after 2 years because of insufficient enrollment. The clinical research coordinator selected patients with a new pathological diagnosis and managed the collected data to limit selection bias. Odds ratio (OR) or confidence intervals (CI) were calculated using a logistic regression model. Multiple imputation was used to analyze missing data regarding the exposure and outcome variables and the five combined imputed datasets using Rubin's rule (17). We used R software (version 3.6.3; R Core Team, R Foundation for Statistical Computing, Vienna, Austria) and the "mice" package (version 3.8.0) for the analyses. We performed sensitivity analyses comparing multivariate analysis with multiple imputation and complete case analysis. P values of <0.05 were considered statistically significant.

Results

Diagnostic method

The study enrolled 264 patients who fulfilled the inclusion criteria (*Figure 1*). The patients' characteristics are summarized in *Table 1*. The patients were categorized into

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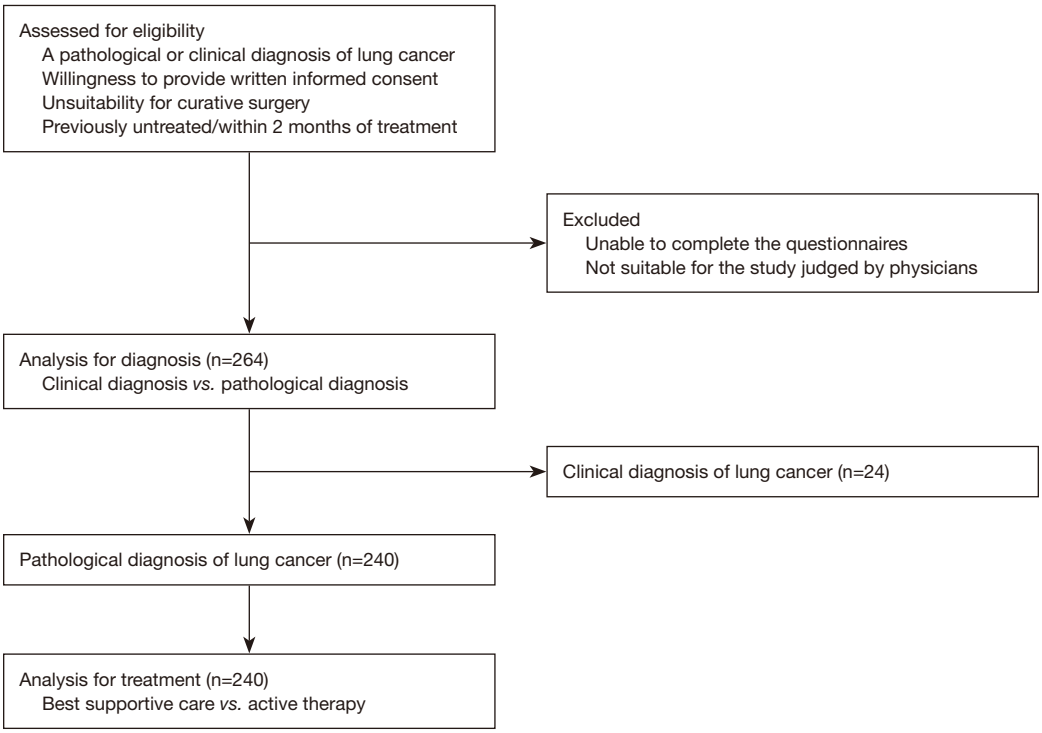

Figure 1 Patient flow chart.

quartile 1 (≤3 points), quartile 2 (≥4, ≤6 points), quartile 3 (7 points), and quartile 4 (≥8 points) based on the UCLA loneliness scale score, and each group included 70 (26%) patients, 109 (41%) patients, 39 (15%) patients, and 41 (16%) patients. The clinically diagnosed group included 24 patients, and the pathologically diagnosed group included 240 patients. Except for driver gene mutation and PD-L1, which are not mandatory for all patients, the proportion of missing data was <3% in each confounding factor because of an incomplete questionnaire. The univariate analysis revealed that a clinical diagnosis was not significantly associated with loneliness (quartile 4 *vs.* quartile 1, OR: 0.19, 95% CI: 0.02–1.60; quartile 3 *vs.* quartile 1, OR: 1.70, 95% CI: 0.56–5.10; quartile 2 *vs.* quartile 1, OR: 0.61, 95% CI: 0.22–1.72). Furthermore, a clinical diagnosis was not significantly associated with social isolation (present *vs.* absent, OR: 0.72, 95% CI: 0.31–1.69) (*Table 2*). Moreover, multivariate analysis with multiple imputation revealed that a clinical diagnosis was not significantly associated with loneliness (quartile 4 *vs.* quartile 1, OR: 0.10, 95% CI: 0.01–1.08; quartile 3 *vs.* quartile 1, OR: 1.36, 95% CI: 0.35–5.37; quartile 2 *vs.* quartile 1, OR: 0.49, 95% CI: 0.14–1.67) or with social isolation (OR: 1.82, 95% CI: 0.60–5.56) (*Table 2*). The complete case analysis also revealed the same results (*Table 2*).

Initial treatment

The analysis of initial treatment included 240 patients with pathologically diagnosed lung cancer (*Table 3*). The loneliness scores were used to assign the patients to quartile 1 (62 patients, 26%), quartile 2 (101 patients, 42%), quartile 3 (32 patients, 13%), and quartile 4 (40 patients, 17%), while 5 patients were excluded because of incomplete answers. Social isolation was judged to be present for 79 patients (33%) and absent for 153 patients (64%), although 8 patients were excluded because of incomplete answers (*Table 3*).

BSC group included 27 patients, and the pathologically diagnosed group included 213 patients. The univariate analysis revealed that the use of BSC as the initial treatment was not significantly associated with loneliness (quartile 4 *vs.* quartile 1, OR: 0.96, 95% CI: 0.29–3.19; quartile 3 *vs.* quartile 1, OR: 0.70, 95% CI: 0.17–2.83; quartile 2 *vs.* quartile 1, OR: 0.82, 95% CI: 0.31–2.18) or with social

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Table 1 Characteristics of the study participants about clinical diagnosis

Characteristic	All cases	Loneliness					Social isolation			Missing data
		q1 (≤3)	q2 (≥4, ≤6)	q3 [7]	q4 (≥8)	Unclassified[†]	Absent (≥12)	Present (<12)	Unclassified[†]	
Cases	264	70 (26%)	109 (41%)	39 (15%)	41 (16%)	5 (2%)	89 (34%)	167 (63%)	8 (3%)	
Sex										
Male	206 (78%)	48 (69%)	90 (83%)	27 (69%)	36 (69%)	5 (100%)	74 (83%)	125 (75%)	7 (88%)	
Female	58 (22%)	22 (31%)	19 (17%)	12 (31%)	5 (31%)	0 (0%)	15 (17%)	42 (25%)	1 (12%)	
Age (years)[‡]	72.2±9.4	72.7±11.2	72.3±8.4	72.8±8.6	70.1±9.0		71.6± 8.6	72.9±9.3		
Smoking status (current or previous)	235 (89%)	56 (80%)	101 (93%)	34 (87%)	39 (95%)	5 (100%)	83 (93%)	145 (87%)	7	
Respiratory symptoms	152 (58%)	39 (56%)	65 (60%)	24 (62%)	22 (53%)	2 (40%)	53 (60%)	94 (56%)	5 (63%)	8 (3%)
Weight loss	85 (32%)	19 (27%)	39 (36%)	11 (28%)	16 (39%)	4 (80%)	34 (38%)	49 (29%)	2 (25%)	2 (1%)
Found with any symptoms	152 (58%)	42 (60%)	58 (53%)	25 (64%)	24 (59%)	3 (60%)	59 (66%)	88 (53%)	5 (63%)	
Dementia	131 (50%)	30 (48%)	51 (50%)	26 (67%)	24 (59%)	0 (0%)	49 (55%)	78 (47%)	4 (50%)	1 (1%)
ECOG performance status score										
0	59 (22%)	18 (26%)	23 (21%)	9 (23%)	9 (22%)	0 (0%)	15 (17%)	43 (26%)	1 (13%)	
1	138 (52%)	36 (51%)	56 (51%)	21 (54%)	20 (48%)	5 (100%)	46 (52%)	89 (53%)	3 (38%)	
2	36 (14%)	8 (11%)	17 (16%)	4 (10%)	7 (17%)	0 (0%)	16 (18%)	18 (11%)	2 (25%)	
3	23 (9%)	6 (9%)	10 (9%)	4 (10%)	3 (7%)	0 (0%)	9 (10%)	13 (8%)	1 (13%)	
4	8 (3%)	2 (3%)	3 (3%)	1 (3%)	2 (5%)	0 (0%)	3 (3%)	4 (2%)	1 (13%)	
Histology										
Squamous	60 (22%)	10 (11%)	24 (26%)	10 (26%)	14 (34%)	2 (40%)	27 (30%)	31 (19%)	2 (25%)	
Non-squamous	125 (47%)	44 (63%)	49 (45%)	12 (31%)	18 (44%)	2 (40%)	31 (35%)	88 (53%)	6 (75%)	
SCLC	55 (21%)	8 (11%)	28 (26%)	10 (26%)	8 (20%)	1 (20%)	21 (24%)	34 (20%)	0 (0%)	
Stage										3 (1%)
I	19 (7%)	4 (6%)	6 (6%)	6 (15%)	2 (5%)	1 (20%)	3 (3%)	16 (10%)	0 (0%)	
II	20 (7%)	5 (7%)	10 (9%)	3 (8%)	2 (5%)	0 (0%)	4 (4%)	15 (9%)	1 (13%)	
III	77 (30%)	22 (31%)	31 (28%)	11 (28%)	12 (29%)	1 (20%)	29 (33%)	47 (28%)	1 (13%)	
IV	145 (55%)	39 (56%)	60 (55%)	18 (46%)	25 (61%)	3 (60%)	50 (56%)	89 (53%)	6 (75%)	

Table 1 (*continued*)

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Table 1 *(continued)*

Characteristic	All cases	Loneliness					Social isolation			Missing data
		q1 (≤3)	q2 (≥4, ≤6)	q3 [7]	q4 (≥8)	Unclassified†	Absent (≥12)	Present (<12)	Unclassified†	
Targetable driver gene mutation										
EGFR positive	24 (9%)	14 (20%)	5 (5%)	1 (3%)	3 (7%)	1 (20%)	6 (6%)	17 (10%)	1 (13%)	147 (56%)
EML4-ALK positive	7 (3%)	4 (6%)	3 (3%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	6 (4%)	1 (13%)	155 (59%)
ROS1 positive	1 (0.4%)	1 (1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.6%)	0 (0%)	163 (58%)
PD-L1 (≥1%)	114 (43%)	32 (46%)	47 (43%)	11 (28%)	22 (54%)	2 (40%)	41 (46%)	67 (40%)	6 (75%)	108 (41%)

Loneliness was evaluated with Japanese Version 3 of the UCLA (University of California, Los Angeles) Loneliness Scale. Higher score means worse loneliness. Patients were divided into quartiles. Social isolation was evaluated with Japanese version of the Lubben Social Network Scale (LSNS-6). Patients were divided by the cutoff of English version. †, unclassified due to incomplete answer; ‡, mean ± standard deviation (SD). q, quartile; ECOG, Eastern Cooperative Oncology Group; SCLC, small cell lung cancer; EGFR, epidermal growth factor receptor; EML-4, echinoderm microtubule-associated protein-like 4; ALK, anaplastic lymphoma kinase; PD-L1, programmed death-ligand 1.

isolation (present *vs.* absent, OR: 0.61, 95% CI: 0.27–1.37) (*Table 4*). Furthermore, multivariate analysis with multiple imputation revealed that BSC was not significantly associated with loneliness (quartile 4 *vs.* quartile 1, OR: 0.41, 95% CI: 0.06–2.72; quartile 3 *vs.* quartile 1, OR: 0.75, 95% CI: 0.12–4.78; quartile 2 *vs.* quartile 1, OR: 0.44, 95% CI: 0.10–1.89) or with social isolation (OR: 1.19, 95% CI: 0.39–3.70) (*Table 4*). The complete case analysis also revealed the same results (*Table 4*).

Discussion

The present study revealed that loneliness and social isolation did not appear to influence the determination of a passive clinical diagnosis and treatment of Japanese patients with advanced lung cancer. A systematic review has indicated that social isolation increases all-cause mortality (5), although we are not aware of any studies regarding the effects of loneliness and social isolation on cancer-related outcomes. Some studies have evaluated the relationships of diagnosis or treatment with education and economic status, which are downstream to loneliness and social isolation as SDH factors (7-9). Pezzi *et al.* reported that government insurance coverage was not related to chemotherapy use but was associated with decreased radiotherapy use (8). This may indicate that social interactions, which are reflected in loneliness and social isolation, may influence cancer diagnosis or treatment. However, the present study revealed that loneliness and social isolation were not associated with lung cancer diagnosis and treatment in Japan. This result may be related to the universal health insurance system in Japan, which may limit the effects of these factors on lung cancer diagnosis and treatment selection (18). We will follow the enrolled patients to monitor their outcomes.

The present study's findings might not be applicable to countries without a universal health insurance system. For example, American lung cancer patients living in high deprivation areas have lower rates of surgical treatment (19). In addition, stage I–III non-small cell lung cancer patients are more likely to receive timely treatment at a private hospital than at a public hospital (20), and uninsured status is also associated with a lower initial treatment rate for small cell lung cancer in the US (8). Thus, physicians might be more aware of their patients' socio-economic conditions if they are not covered by a universal health insurance system, and active treatment might be less common for socially isolated or lonely patients in that setting.

Most of the studies about SDHs were conducted in

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Table 2 Univariate analysis/multivariate analysis with multiple imputation/complete case analysis of clinical diagnosis with loneliness and social isolation

Loneliness/social isolation	Univariate analysis		Multivariate analysis (multiple imputation)		Multivariate analysis (complete case analysis)	
	OR	95% CI	OR	95% CI	OR	95% CI
Loneliness						
q1 (≤3)	Reference	Reference	Reference	Reference	Reference	Reference
q2 (>3, ≤6)	0.61	0.22 to 1.72	0.49	0.14 to 1.67	0.36	0.10 to 1.37
q3 [7]	1.70	0.56 to 5.10	1.36	0.35 to 5.37	1.41	0.35 to 4.56
q4 (≥8)	0.19	0.02 to 1.60	0.10	0.01 to 1.08	0.11	0.01 to 4.55
Social isolation						
Absent (≥12)	Reference	Reference	Reference	Reference	Reference	Reference
Present (<12)	0.72	0.31 to 1.69	1.82	0.60 to 5.56	0.75	0.22 to 2.54

Analyzed with logistic regression model. Loneliness was evaluated with Japanese Version 3 of the UCLA (University of California, Los Angeles) Loneliness Scale. Higher score means worse loneliness. Patients were divided into quartiles. Social isolation was evaluated with Japanese version of the Lubben Social Network Scale (LSNS-6). Patients were divided by the cutoff of English version. Variables used for adjustment of multivariate analysis/complete case analysis were sex (male *vs.* female), age (≥75 *vs.* <75), smoking status (current/previous *vs.* never), found with any symptoms (positive *vs.* negative), dementia (present *vs.* absent), Eastern Cooperative Oncology Group (ECOG) performance status score (≥2 *vs.* ≤1) and stage (≥IIIB *vs.* ≤IIIA). q, quartile; OR, odds ratio; CI, confidence intervals.

western countries (5-10). However, this is the first study conducted in East Asia, especially in the field of lung cancer. Furthermore, this study's findings are strengthened by the small amount of missing data and the adjustment for clinically relevant confounding factors, which increases the reliability of our findings. However, the present study also had several limitations. First, the enrollment criteria are likely a source of selection bias. Although the clinical research coordinator selected patients with a new pathological diagnosis to limit selection bias, many patients were diagnosed clinically. Therefore, some selection bias still likely remained, such as high-income patients being more inclined to receive advanced treatment at specialized hospitals; the relationship between social factors and prognosis is likely weakened, although our region has a very small population of high-income individuals. Additionally, the patient demography may be biased based on the research derived from a single center. Furthermore, most patients are treated at a hospital near where they live, which suggests that patients at our center are representative of the local population. Second, we did not assess overall survival because of the short survey period (21). We plan to continue the follow-up of our patients for an additional 2 years in order to monitor their long-term outcomes.

In Japan, loneliness and social isolation were not significantly related to the clinical diagnosis or initial treatment of patients with advanced lung cancer. Therefore, physicians and other medical staff may not need to consider these SDH factors when diagnosing lung cancer and selecting treatment. However, further studies are needed to investigate the relationships of loneliness and social isolation with the prognosis of lung cancer patients.

Conclusions

In Japan, loneliness and social isolation were not significantly related to the clinical diagnosis or initial treatment of patients with advanced lung cancer. Therefore, physicians and other medical staff may not need to consider these SDH factors when diagnosing lung cancer and selecting treatment. However, further studies are needed to investigate the relationships of loneliness and social

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Table 3 Characteristics of the study participants about best supportive care

Characteristic	All cases	Loneliness					Social isolation			Missing data
		q1 (≤3)	q2 (≥4, ≤6)	q3 [7]	q4 (≥8)	Unclassified[†]	Absent (≥12)	Present (<12)	Unclassified[†]	
Cases	240	62 (26%)	101 (42%)	32 (13%)	40 (17%)	5 (2%)	79 (33%)	153 (64%)	8 (3%)	
Sex										
Male	188 (78%)	43 (70%)	83 (82%)	22 (69%)	35 (88%)	5 (100%)	64 (81%)	117 (76%)	7 (88%)	
Female	52 (22%)	19 (30%)	18 (18%)	10 (31%)	5 (13%)	0 (0%)	15 (19%)	36 (24%)	1 (12%)	
Age (years)[‡]	71.5±9.2	71.5±11.2	71.9±8.3	71.4±7.9	69.8±8.8		71.1±8.7	72.1±9.1		
Smoking status (current or previous)	216 (90%)	49 (79%)	95 (94%)	29 (91%)	38 (95%)	5 (100%)	75 (95%)	134 (88%)	7 (88%)	
Respiratory symptoms	139 (58%)	34 (55%)	61 (60%)	21 (66%)	21 (55%)	2 (40%)	47 (59%)	87 (57%)	5 (63%)	6 (3%)
Weight loss	77 (32%)	16 (26%)	38 (38%)	8 (25%)	15 (38%)	0 (0%)	29 (67%)	46 (30%)	2 (25%)	2 (1%)
Found with any symptoms	142 (59%)	38 (61%)	57 (56%)	21 (66%)	23 (58%)	3 (60%)	54 (68%)	83 (54%)	5 (63%)	
Dementia	115 (48%)	25 (40%)	46 (46%)	21 (66%)	23 (58%)	0 (0%)	43 (54%)	68 (%)	4 (50%)	1 (1%)
ECOG performance status score										
0	54 (23%)	18 (29%)	20 (20%)	7 (22%)	9 (23%)	0 (0%)	14 (18%)	39 (25%)	1 (13%)	
1	134 (59%)	34 (55%)	55 (54%)	20 (63%)	20 (50%)	5 (100%)	44 (56%)	87 (57%)	3 (38%)	
2	31 (13%)	6 (10%)	16 (16%)	2 (6%)	7 (18%)	0 (0%)	15 (19%)	14 (9%)	2 (25%)	
3	16 (7%)	3 (5%)	7 (7%)	3 (9%)	3 (8%)	0 (0%)	4 (5%)	11 (7%)	1 (13%)	
4	5 (2%)	1 (2%)	3 (3%)	0 (0%)	1 (3%)	0	2 (3%)	2 (1%)	1 (13%)	
Histology										
Squamous	60 (25%)	10 (16%)	24 (24%)	10 (31%)	14 (35%)	2 (40%)	27 (34%)	31 (20%)	2 (25%)	
Non-squamous	125 (52%)	44 (71%)	49 (49%)	12 (38%)	18 (45%)	2 (40%)	31 (39%)	88 (58%)	6 (75%)	
SCLC	55 (23%)	8 (13%)	28 (28%)	10 (31%)	8 (20%)	1 (20%)	21 (26%)	34 (22%)	0 (0%)	
Stage										1 (1%)
I	14 (6%)	3 (5%)	4 (4%)	4 (13%)	2 (5%)	1 (20%)	2 (3%)	12 (8%)	0 (0%)	
II	17 (7%)	3 (5%)	10 (10%)	2 (6%)	2 (5%)	0 (0%)	2 (3%)	14 (9%)	1 (13%)	
III	72 (30%)	20 (32%)	29 (29%)	10 (31%)	12 (30%)	1 (20%)	28 (35%)	43 (28%)	1 (13%)	
IV	136 (57%)	36 (58%)	58 (57%)	15 (47%)	24 (60%)	3 (60%)	46 (58%)	84 (55%)	6 (75%)	

Table 3 (*continued*)

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Table 3 (*continued*)

Characteristic	All cases	Loneliness					Social isolation			Missing data
		q1 (≤3)	q2 (≥4, ≤6)	q3 [7]	q4 (≥8)	Unclassified†	Absent (≥12)	Present (<12)	Unclassified†	
Targetable driver gene mutation										
EGFR positive	24 (10%)	14 (23%)	5 (5%)	1 (3%)	3 (8%)	1 (20%)	6 (8%)	17 (11%)	1 (13%)	123 (51%)
EML4-ALK positive	7 (3%)	4 (6%)	3 (3%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	6 (4%)	1 (13%)	131 (55%)
ROS1 positive	1 (0.4%)	1 (2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (1%)	0 (0%)	139 (58%)
PD-L1 (≥1%)	114 (48%)	32 (52%)	47 (47%)	11 (34%)	22 (55%)	2 (40%)	41 (52%)	67 (44%)	6 (75%)	85 (35%)

Loneliness was evaluated with Japanese Version 3 of the UCLA (University of California, Los Angeles) Loneliness Scale. Higher score means worse loneliness. Patients were divided into quartiles. Social isolation was evaluated with Japanese version of the Lubben Social Network Scale (LSNS-6). Patients were divided by the cutoff of English version. †, unclassified due to incomplete answer. ‡, mean ± standard deviation (SD). q, quartile; ECOG, Eastern Cooperative Oncology Group; SCLC, small cell lung cancer; EGFR, epidermal growth factor receptor; EML-4, echinoderm microtubule-associated protein-like 4; ALK, anaplastic lymphoma kinase; PD-L1, programmed death-ligand 1.

Table 4 Univariate analysis/multivariate analysis with multiple imputation/complete case analysis of clinical best supportive care with loneliness and social isolation

Loneliness/social isolation	Univariate analysis		Multivariate analysis (multiple imputation)		Multivariate analysis (complete case analysis)	
	OR	95% CI	OR	95% CI	OR	95% CI
Loneliness						
q1 (≤3)	Reference	Reference	Reference	Reference	Reference	Reference
q2 (>3, ≤6)	0.82	0.31 to 2.18	0.44	0.10 to 1.89	<0.01	0 to inf
q3 [7]	0.70	0.17 to 2.83	0.75	0.12 to 4.78	>100	0 to inf
q4 (≥8)	0.96	0.29 to 3.19	0.41	0.06 to 2.72	<0.01	0 to inf
Social isolation						
Absent (≥12)	Reference	Reference	Reference	Reference	Reference	Reference
Present (<12)	0.61	0.27 to 1.37	1.19	0.39 to 3.70	>100	0 to inf

Analyzed with logistic regression model. Loneliness was evaluated with Japanese Version 3 of the UCLA (University of California, Los Angeles) Loneliness Scale. Higher score means worse loneliness. Patients were divided into quartiles. Social isolation was evaluated with Japanese version of the Lubben Social Network Scale (LSNS-6). Patients were divided by the cutoff of English version. Variables used for adjustment of multivariate analysis/complete case analysis were sex (male *vs.* female), age (≥75 *vs.* <75), smoking status (current/previous *vs.* never), respiratory symptoms (positive *vs.* negative), weight loss (positive *vs.* negative), Eastern Cooperative Oncology Group (ECOG) performance status score (≥2 *vs.* ≤1), stage (≥IIIB *vs.* ≤IIIA). epidermal growth factor receptor (EGFR) mutation (positive *vs.* negative). Echinoderm microtubule-associated protein-like 4 (EML-4) anaplastic lymphoma kinase (ALK) rearrangement (positive *vs.* negative), C-ros oncogene 1 mutation (positive *vs.* negative) and programmed death-ligand 1 tumor proportion score (≥1% *vs.* 0%). q, quartile; OR, odds ratio; CI, confidence intervals.

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isolation with the prognosis of lung cancer patients.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the institutional ethics board of Hyogo Prefectural Amagasaki General Medical Center (# 29-164), and informed consent was taken from all individual participants.

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