Original Article

Factors Predisposing Terminally Ill Cancer Patients' Preferences for Distinct Patterns/States of Life-Sustaining Treatments Over Their Last Six Months

Fur-Hsing Wen, PhD, Jen-Shi Chen, MD, Wen-Chi Chou, MD, Wen-Cheng Chang, MD, Chia-Hsun Hsieh, MD, and Siew Tzuh Tang, DNSc

Department of International Business (F.-H.W.), Soochow University, Taipei, Taiwan; Division of Hematology-Oncology (J.-S.C., W.-C.Chou, W.-C.Chang, C.-H.H., S.T.T.), Chang Gung Memorial Hospital at Linkou, Tao-Yuan, Taiwan; Chang Gung University College of Medicine (J.-S.C., W.-C.Chou, W.-C.Chang, C.-H.H.), Tao-Yuan, Taiwan; and Department of Nursing (S.T.T.), Chang Gung Memorial Hospital at Kaohsiung, Kaohsiung, Taiwan, R.O.C

Abstract

Context. High-quality end-of-life (EOL) care depends on thoroughly assessing terminally ill patients' preferences for EOL care and tailoring care to individual needs. Studies on predictors of EOL-care preferences were primarily cross-sectional and assessed preferences for multiple life-sustaining treatments (LSTs), making clinical applications difficult.

Objective/Methods. We examined factors predisposing cancer patients ($N = 303$) to specific LST-preference states (life-sustaining preferring, comfort preferring, uncertain, and nutrition preferring) derived from six LSTs (cardiopulmonary resuscitation, intensive care unit care, chest compression, intubation with mechanical ventilation, intravenous nutrition, and tube feeding) in patients' last six months by multilevel multinomial logistic regression.

Results. Participants with accurate prognostic awareness and physician-patient EOL-care discussions were less likely to be in life-sustaining-preferring, uncertain, and nutrition-preferring states than in the comfort-preferring state. Better quality of life (QOL) and more depressive symptoms predisposed participants to be less likely to be in the uncertain than in the comfort-preferring state. Membership in the nutrition-preferring rather than the comfort-preferring state was significantly higher for participants in the state of moderate symptom distress with severe functional impairment than in the state of mild symptom distress with high functioning.

Conclusion. Accurate prognostic awareness, physician-patient EOL-care discussions, QOL, depressive symptoms, and symptom-functional states predisposed terminally ill cancer patients to distinct LST-preference states. Clinicians should cultivate patients' accurate prognostic awareness and facilitate EOL-care discussions to foster realistic expectations of LST efficacy at EOL. Clinicians should enhance patients' QOL to reduce uncertainty in EOL-care decision making and provide adequate psychological support to those with more depressive symptoms who prefer comfort care only. J Pain Symptom Manage 2019;57:190−198.

Key Words

Life-sustaining treatment preferences, prognostic awareness, end-of-life care discussions, depressive symptoms, symptom distress, functional impairment, end-of-life

Introduction

Facilitating accurate prognostic awareness and eliciting patients' treatment preferences to provide value-concordant care is key to high-quality patient-centered end-of-life (EOL) care,[1,2] whereas neglecting patients' preferences is considered a medical error.[3] However, prognostic disclosure and discussions of EOL-care goals and preferences tend to occur late in

Address correspondence to: Siew Tzuh Tang, DNSc, School of Nursing, Chang Gung University, 259 Wen-Hwa 1st Road, Kwei-Shan, Tao-Yuan, Taiwan 333, R.O.C. E-mail: sttang0619@gmail.com

Accepted for publication: November 7, 2018.

0885-3924/$ - see front matter
https://doi.org/10.1016/j.jpainsymman.2018.11.008

patients' terminal-illness trajectory or not at all.[4] This paradigm should be shifted[5,6] to early, thorough assessments of patients' goals and preferences, clarifying overexpectations of life-sustaining-treatment (LST) efficacy at EOL,[7,8] and tailoring EOL care to individual needs throughout the dying process. This new paradigm may personalize EOL care[5] and counteract the worldwide trend toward aggressive and costly EOL-cancer care,[9] making national economies and health care systems sustainable[10,11] because EOL-care preferences are significantly associated with EOL care received.[12–14]

Seriously/terminally ill patients' EOL-care preferences have been widely studied,[4,13–17] and the stability of these preferences over time is well established,[18] but substantial minorities of patients' preferences fluctuate with changes in their physical/emotional state.[18–21] To avoid futile and expensive LSTs, determinants of LST preferences should be longitudinally examined to target patients who prefer or are uncertain about LSTs to clarify misunderstandings about or overexpectations of LST efficacy at EOL,[7,8] thereby achieving value-concordant EOL care.[1,2]

Clinically modifiable determinants of EOL-care preferences found in cross-sectional studies include prognostic awareness,[16,22–25] EOL-care discussions,[13,26–28] quality of life (QOL),[29] emotional distress,[18,25,29–31] physical functioning,[13,17,32] and symptom burden.[32] Advanced cancer patients with accurate prognostic awareness prefer symptom-directed EOL care over life-prolonging treatments[22–24] and not receiving LSTs at EOL,[22,24] whereas elderly patients without accurate prognostic awareness but with overexpectations of LST efficacy preferred cardiopulmonary resuscitation (CPR)[25] and mechanical ventilation.[16] Cancer patients who discuss EOL-care preferences with their physicians tend to strive for quality rather than quantity of life,[27] value comfort oriented over life-extending EOL care,[13,26,28] but oppose dying in an intensive care unit (ICU)[26,28] and receiving CPR, intubation, and mechanical ventilation support.[28] QOL[29] and symptom burden[32] were not associated with LST preferences. Mixed results were reported for emotional distress and physical functioning. Depressive symptoms have been associated with preferring to forgo CPR,[25,29] not associated with LST preferences,[30,31] or preferring more LSTs.[18] Better physical functioning predisposed terminally ill patients to prefer more aggressive LSTs[17,32] or was not associated with LST preferences.[13] However, cross-sectional studies cannot disentangle the directionality of associations between EOL-care preferences and the aforementioned variables.

The roles played by these variables, which are amenable to effective care/treatments,[33–35] in terminally ill cancer patients' LST preferences as death approaches remain largely unknown because the variables have seldom been longitudinally explored.[19,21,32,36] We note that the conclusion about less aggressive EOL-care preferences being associated with prognostic awareness and physician-patient EOL-care discussions has been reached only in cross-sectional studies,[13,16,22–28] except one.[36] Conflicting results from longitudinal studies were reported for QOL,[19,21] depressive symptoms,[18,19,36] and physical functioning.[19,21,32] Of note, despite symptom distress and functional impairment being common manifestations of cancer patients' terminal illness,[37] few studies directly explored the roles played by increasing symptom distress[32] or functional decline[19,21,32] in determining patients' EOL-care preferences, let alone their conjoint symptom distress and functional impairment, which do not necessarily deteriorate synchronously at EOL.[38–40]

In addition, applying research findings based on assessing preferences for multiple LSTs[18,32,36] in busy clinical care settings may be complicated and impractical. Health care professionals can parsimoniously identify LST-preference patterns/states[41] rather than focusing on individual LSTs, thus minimizing the time spent assessing LST preferences and avoiding troubling terminally ill patients with choosing among multiple individual LSTs when they are physically and psychologically frail as death approaches. Therefore, the purpose of this study was to extend our previous reports[41,42] to identify factors predisposing terminally ill cancer patients to prefer a specific pattern/state of LSTs in their last six months, with a focus on variables that are potentially amenable to effective clinical care/treatments.

Methods

Design and Sample

This secondary analysis study used data from a longitudinal study on the quality of death and dying for terminally ill Taiwanese cancer patients.[36] Factors associated with patients' subject-specific preferences for CPR, ICU care, and intubation with mechanical ventilation over their last year have been identified.[36] The final sample comprised participants who were recruited by convenience in 2009–2012 and died through 2015, with repeated assessments to supply sufficient data.[41] Detailed methods were reported for sampling[41] and identifying distinct LST-preference states.[41,42] Briefly, adult cancer patients were referred by their primary oncologist who recognized their disease as progressive and unresponsive to curative treatments and identified them as terminally ill but cognitively competent to participate. Trained, experienced oncology nurses interviewed participants while hospitalized (baseline assessment) and approximately every two to four weeks thereafter when they were

hospitalized or returned for clinical care to collect all data until they declined participation or died. Because this was an observational study, study participants' primary oncologists were not informed about participants' responses, including their LST preferences and desire for EOL-care discussions with their physician.

Measures

Outcome Variable. Preferences for life-sustaining treatments (i.e., CPR, ICU care, chest compression, intubation with mechanical ventilation, intravenous nutrition support, and nasogastric tube feeding) were assessed using an adapted interview protocol (Appendix 1). For each LST, participants were asked whether they 1) wanted, 2) did not want, or 3) were undecided about the treatment. For these participants, we previously identified four LST-preference states: life-sustaining preferring, comfort preferring, uncertain, and nutrition preferring.[42] These four states reflect participants' uniform preference, uniform rejection, and uniform uncertainty about the six LSTs examined, and their preference for nutrition support by either intravenous supply or tube-feeding but rejection of other treatments, respectively.[42]

Predictors of Distinct States of Life-Sustaining-Treatment Preferences. Potential predictors included both time-varying, clinically modifiable variables (accurate prognostic awareness,[16,22–25,36] physician-patient EOL-care discussions,[13,26–28] QOL,[19,21,29] emotional distress,[8,19,25,29–31,36] and physical symptom distress[32] and functioning),[13,17,19,21,32] and time-invariant patient demographics (gender, age, educational attainment) and disease characteristics (comorbidities, time since diagnosis at enrollment).[18] All instruments selected for time-varying, clinically modifiable variables have been validated and extensively used in the principal investigator's research since 2002 to test hypothesized relationships between concepts measured.[24,28,36,43]

Prognostic awareness was evaluated by asking participants if they knew their prognosis, and if so, whether the disease 1) was curable; 2) might recur in the future, but their life was not currently in danger; and 3) could not be cured, and they would probably die soon. Participants were recognized as accurately understanding their prognosis only if they chose Option 3.[24,36]

Physician-patient EOL-care discussions were measured by asking participants, "Have you and your doctor discussed what kind of care you would want if your disease continued to progress, your condition continually deteriorated, and you were dying? This care includes being resuscitated, receiving treatments if your heart stopped beating or if you could not breathe on your own, or being kept comfortable without aggressive treatments."[28] For baseline and follow-up assessments of physician-patient EOL-care discussions, patients were asked whether such discussions occurred since their diagnosis of advanced cancer and since their last assessment, respectively. Responses were coded 1 (yes) and 0 (no).

Quality of life was measured by a modified McGill Quality of Life Questionnaire (MQOL).[44] The original 16-item MQOL encompasses physical, psychological, social, and existential well-being. The MQOL was modified by omitting three items (the three most distressing symptoms), but retaining the item on overall physical well-being to avoid overlap with the well-established effect of physical symptom distress on participants' QOL. Total scores for the 13-item modified MQOL range = 0−130; higher scores indicate better QOL.

Emotional distress (anxiety and depressive symptoms) was measured by anxiety and depression subscales of the Hospital Anxiety and Depression Scale (HADS), respectively.[45] Total anxiety (HADS-A) and depression (HADS-D) subscale scores range = 0−21; higher scores indicate greater anxiety and depressive symptoms, respectively.[45]

Physical Symptom Distress and Functioning. Physical symptom distress from cancer patients' common symptoms (e.g., pain, dyspnea, anorexia, and insomnia) was measured using the 13-item Symptom Distress Scale.[46] Symptom Distress Scale scores range from 13 to 65; higher scores indicate greater symptom distress. Physical functioning was assessed by the 10-item Enforced Social Dependency Scale.[47] Enforced Social Dependency Scale scores range from 10 to 51; higher scores reflect greater impairment in personal and social functioning. For these participants, we identified five distinct worsening conjoint symptom-functional states[48]: 1) mild symptom distress with high functioning, 2) moderate symptom distress with mild functional impairment, 3) severe symptom distress with moderate functional impairment, 4) moderate symptom distress with severe functional impairment, and 5) profound symptom distress and functional impairment. These conjoint symptom-functional states have been associated with terminally ill cancer patients' survival,[48] QOL, and psychological distress[49] and with these patients' primary caregivers' subjective caregiving burden, QOL, and depressive symptoms.[50]

Comorbidities were calculated by the Deyo-Charlson comorbidity index,[51] categorized as 0, 1, 2, or ≥3 comorbid conditions.

Time proximity to patient death, the period between assessment and death, was used to explore

longitudinal changes in LST-preference states in participants' last six months. This period was categorized as 1−30, 31−90, and 91−180 days.[14]

Statistical Analysis

Factors predisposing terminally ill cancer patient participants to prefer a specific pattern/state of LSTs were examined using hierarchical generalized linear modeling (HGLM)[52] with multilevel multinomial logistic regression and the comfort-preferring state as reference. HGLM accounts for the common characteristics of longitudinal studies, including different waves or times of data collection across participants to accommodate uneven numbers of follow-up assessments and varying time intervals for subsequent data collections.[52] HGLM uses random intercepts to account for within-subject correlations of repeated observations from each participant.[52] Our HGLM analysis modeled the outcome variable (a specific LST-preference state in reference to the comfort-preferring state) as a function of proposed lagged time-varying predictors (accurate prognostic awareness, physician-patient EOL-care discussions, QOL, emotional distress, and symptom-functional states) in the previous wave of assessment. The lagged measures were added to identify factors associated with a specific LST-preference state by arranging time-varying, clinically modifiable variables and LST-preference states in a distinct time sequence to ensure a clear time sequence. The regression parameter for each independent variable was exponentiated to transform into adjusted odds ratio (AOR) with 95% CI.

Results

Sample Characteristics

Sample characteristics have been reported.[41] Participants were predominantly male (56.8%), were married (80.5%), with a mean (SD) age of 58.5 (12.8) years, and had been educated to ≤ junior high school (59.1%). Participants' most common diagnoses were liver (18.5%), stomach (17.5%), pancreas (13.9%), lung (10.9%), and head and neck (8.9%) cancer. After enrollment, participants survived a median of 94 days (mean [SD] = 168.4 [206.1]; range = 3−1506) and completed a median of 5.0 follow-up assessments (mean [SD] = 5.2 [3.2]; range = 1−12) in their last six months about 18.5 days (SD = 7.6; median = 15; range = 4−82) apart. Participants' last assessment was on average 26.2 days (SD = 26.0; median = 18.0; range = 1−166) before death. Proportions of participants with accurate prognostic awareness and physician-patient EOL-care discussions as well as scores for QOL, anxiety and depressive symptoms, physical symptom distress, and physical functioning across the four identified LST-preference states are presented in Table 1. Changes in the prevalences of accurate prognostic awareness and physician-patient EOL-care discussions versus time proximity to death are in Appendix 2.

Factors Predisposing Preferences for Specific States of Life-Sustaining Treatments in Reference to the Comfort-Preferring State in the Last Six Months. Our multilevel multinomial logistic regression conducted by HGLM showed that, after controlling for selected time-invariant and time-varying variables, LST-preference

Table 1

Proportions of Terminally Ill Cancer Patients With Accurate Prognostic Awareness and Physician-Patient EOL Care Discussions and Levels of QOL, Emotional Distress, Physical Symptom Distress, and Physical Functioning Across Four LST Preferences States

Parameter	LST-Preference State			
	Life-Sustaining Preferring	Comfort Preferring	Uncertain	Nutrition Preferring
Average state size (%)	8.7	47.9	19.9	23.5
With accurate prognostic awareness (%)	52.6	81.7	61.6	70.8
With physician-patient EOL-care discussions (%)	5.2	15.5	7.5	11.9
Quality of life (MQOL score; M [SD])	91.4 (23.2)	84.0 (24.3)	79.7 (24.2)	78.4 (27.1)
Anxiety symptoms (HADS-A score; M [SD])	7.0 (4.7)	7.4 (4.5)	7.5 (4.8)	8.7 (5.0)
Depressive symptoms (HADS-D score; M [SD])	12.9 (5.2)	12.6 (5.7)	11.5 (5.7)	13.2 (6.0)
Physical symptom distress (SDS score; M [SD])	30.0 (9.5)	29.9 (9.1)	26.3 (7.7)	29.8 (9.2)
Physical functioning (ESDS score; M [SD])	28.4 (9.9)	27.8 (10.0)	27.0 (9.7)	29.6 (9.8)
Symptom-functional state (%)				
1	13.4	15.6	19.0	11.4
2	29.9	31.4	32.4	24.4
3	15.7	17.4	11.1	19.1
4	23.1	14.7	27.5	27.4
5	17.9	20.8	10.1	17.7

EOL = end-of-life; QOL = quality of life; LST = life-sustaining treatment; MQOL = McGill Quality of Life Questionnaire; HADS-A = Hospital Anxiety and Depression Scale−Anxiety subscale; HADS-D = Hospital Anxiety and Depression Scale−Depression subscale; SDS = Symptom Distress Scale; ESDS = Enforced Social Dependency Scale.

Symptom-functional states: 1) mild symptom distress with high functioning, 2) moderate symptom distress with mild functional impairment, 3) severe symptom distress with moderate functional impairment, 4) moderate symptom distress with severe functional impairment, and 5) profound symptom distress and functional impairment.

states did not change significantly in participants' last six months (Table 2). Participants with accurate prognostic awareness were less likely than those without such awareness to be in the life-sustaining preferring (AOR [95% CI] = 0.096 [0.045−0.205]), uncertain (AOR [95% CI] = 0.234 [0.121−0.450]), and nutrition preferring (AOR [95% CI] = 0.263 [0.143−0.485]) states than in the comfort-preferring state in the next assessment. Similarly, participants who reported having discussed EOL-care issues with their primary oncologist were significantly less likely than those without EOL-care discussions to be in the other three LST-preference states than in the comfort-preferring state.

However, QOL and depressive-symptom levels in the previous wave of assessment were associated with the likelihood of being in the uncertain state only in reference to the comfort-preferring state. Higher QOL levels (AOR [95% CI] = 0.978 [0.963−0.993] with each unit increase in MQOL score) and depressive-symptom levels (AOR [95% CI] = 0.918 [0.852−0.989] with each unit increase in HADS-D score) predisposed participants to be significantly less likely to be in the uncertain state than in the comfort-preferring state in the next assessment. The likelihood of being in the nutrition-preferring state in reference to the comfort-preferring state was significantly higher for participants who in the previous assessment wave were in the state of moderate symptom distress with severe functional impairment (AOR [95% CI] = 3.694 [1.159−11.776]) than for participants in the best state of mild symptom distress

Table 2

Factors Predisposing Terminally Ill Cancer Patients' Preferences for Specific States of Life-Sustaining Treatments in Reference to the Comfort-Preferring State in Their Last Six Months

	Life-Sustaining Preferring				Uncertain				Nutrition Preferring			
Factor	AOR	95% CI		*P*	AOR	95% CI		*P*	AOR	95% CI		*P*
Time proximity to death (days)												
≤30	Ref				Ref				Ref			
31−90	1.281	0.660	2.485	0.465	1.064	0.601	1.884	0.832	0.742	0.448	1.227	0.245
91−180	0.955	0.391	2.332	0.919	1.695	0.818	3.512	0.156	0.717	0.359	1.431	0.246
Accurate prognostic awareness												
Yes	**0.096**	**0.045**	**0.205**	**<0.001**	**0.234**	**0.121**	**0.450**	**<0.001**	**0.263**	**0.143**	**0.485**	**<0.001**
No	Ref				Ref				Ref			
Physician-patient end-of-care discussions												
Yes	**0.329**	**0.109**	**0.997**	**0.050**	**0.388**	**0.164**	**0.915**	**0.031**	**0.205**	**0.086**	**0.492**	**<0.001**
No	Ref				Ref				Ref			
Quality of life[a]	1.016	0.993	1.038	0.174	**0.978**	**0.963**	**0.993**	**0.005**	0.989	0.976	1.002	0.088
Anxiety symptoms[b]	1.058	0.945	1.184	0.328	1.034	0.955	1.118	0.421	1.015	0.952	1.081	0.653
Depressive symptoms[c]	0.995	0.906	1.092	0.909	**0.918**	**0.852**	**0.989**	**0.024**	0.957	0.885	1.035	0.269
Lagged symptom-functional state[d]												
1	Ref				Ref				Ref			
2	1.623	0.438	6.009	0.469	1.291	0.456	3.660	0.631	1.228	0.464	3.251	0.679
3	1.634	0.342	7.810	0.583	0.446	0.094	2.116	0.310	1.766	0.581	5.371	0.316
4	3.718	0.660	20.939	0.137	1.723	0.427	6.956	0.445	**3.694**	**1.159**	**11.776**	**0.027**
5	2.120	0.291	15.453	0.459	0.924	0.175	4.886	0.926	2.100	0.540	8.169	0.285
Gender												
Male	1.750	0.482	6.351	0.395	1.080	0.425	2.744	0.871	1.154	0.481	2.772	0.749
Female	Ref				Ref				Ref			
Age	0.991	0.940	1.043	0.719	1.009	0.969	1.052	0.660	0.973	0.933	1.013	0.185
Educational attainment												
<Senior high school	0.807	0.197	3.312	0.767	1.763	0.642	4.847	0.273	2.187	0.818	5.845	0.120
≥Senior high school	Ref				Ref				Ref			
Comorbidities[e]												
0	Ref				Ref				Ref			
1	0.370	0.085	1.614	0.187	0.300	0.098	0.920	0.036	0.393	0.136	1.138	0.086
2	0.315	0.055	1.805	0.196	0.449	0.115	1.750	0.250	0.645	0.178	2.342	0.506
≥3	0.163	0.022	1.219	0.819	0.123	0.024	0.620	0.012	0.594	0.156	2.263	0.446
Time since cancer diagnosis (months)												
≤6	Ref				Ref				Ref			
7−12	1.202	0.250	5.786	0.819	1.977	0.575	6.794	0.280	1.573	0.496	4.983	0.442
13−24	0.545	0.092	3.233	0.504	0.436	0.111	1.711	0.235	0.876	0.258	2.977	0.832
>24	0.208	0.035	1.237	0.085	0.721	0.209	2.486	0.605	0.326	0.098	1.086	0.069

AOR = adjusted odds ratio; Ref = reference.
Bold indicates statistical significance.
[a]McGill Quality of Life Questionnaire score.
[b]Hospital Anxiety and Depression Scale−Anxiety subscale score.
[c]Hospital Anxiety and Depression Scale−Depression subscale score.
[d]Symptom-functional states: 1) mild symptom distress with high functioning, 2) moderate symptom distress with mild functional impairment, 3) severe symptom distress with moderate functional impairment, 4) moderate symptom distress with severe functional impairment, and 5) profound symptom distress and functional impairment.
[e]Deyo-Charlson comorbidity index.

with high functioning. No other associations were observed between distinct symptom-functional states and the likelihood of subsequently being in any LST-preference state. LST-preference states were not associated with participants' demographics (gender, age, educational attainment) or disease characteristics (comorbidities, time since diagnosis at enrollment).

Discussion

Our prospective, longitudinal study found that terminally ill Taiwanese cancer patients' LST preferences (categorized as four identified distinct states) did not change significantly in their last six months. This result, obtained by examining changes in LST-preference states close to the patient's death, verifies evidence that EOL-care preferences for terminally or critically ill patients remain stable over time.[18] Terminally ill cancer patients' membership in a specific LST-preference state in the subsequent assessment was predisposed by their accurate prognostic awareness, physician-patient EOL-care discussions, QOL, depressive symptoms, and symptom-functional states.

Our longitudinal study confirmed cross-sectional associations between accurate prognostic awareness or physician-patient EOL-care discussions and preferences for symptom-directed EOL care over life-prolonging treatments[13,22–24,26,28] by showing that terminally ill Taiwanese cancer patients with accurate prognostic awareness or physician-patient EOL-care discussions in the previous wave of assessment were significantly more likely to be in the comfort-preferring state (uniformly rejecting all six LSTs examined) than in life-sustaining-preferring, uncertain, or nutrition-preferring states. Accurate prognostic awareness and appropriate physician-patient EOL-care discussions are prerequisites for terminally ill cancer patients to actively engage in advance care planning[53] and to realistically appraise LST efficacy at EOL,[7,23] thereby predisposing them to reject futile LSTs (not only aggressive LSTs like CPR, ICU care, and mechanical ventilation, but also potentially bothersome nutrition support)[32,54] and reducing uncertainty about their LST preferences.

The novelty of our findings lies in participants' higher QOL and depressive symptom levels predisposing them to be significantly less likely to be in the uncertain state than in the comfort-preferring state in the next assessment. By contrast, existing studies show that depression predisposes terminally/critically ill patients to reject,[19,25,29,36] accept,[18] or not be associated with[30,31] LST preferences, whereas QOL is not[29] or positively[19,21] associated with rejection of LSTs. However, in these studies except one,[36] uncertainty was not an option or was omitted.[21] Our result confirms our previous observation that more depressive symptoms decreased terminally ill cancer patients' likelihood of uncertainty about preferences for ICU care and mechanical ventilation support than rejecting such LSTs.[36]

Our results suggest that better QOL and more depressive symptoms reduce terminally ill cancer patients' uncertainty in choosing their preferred LSTs. Decisional uncertainty may reflect patients' lack of knowledge about and understanding of the clinical situation or the risks and benefits inherent in each EOL-care decision, and their inability to project their preferences into the future,[55] especially for unfamiliar situations[56] as one's own death and dying. We speculate that enjoying better QOL reassures terminally ill cancer patients that the *status quo* is good enough not to be bothered by the unnecessary suffering caused by additional LSTs, whereas greater pessimism about one's future may lead to giving up fighting one's disease via LSTs. Both conditions (better QOL and more depressive symptoms) may reduce terminally ill patients' ambivalence about LSTs when making EOL-care decisions. However, our speculation warrants further validation to avoid Type I errors derived from multiple comparisons across the four distinct LST-preference states, preferably by qualitative studies to thoroughly understand the mechanisms by which better QOL and more depressive symptoms reduce uncertainty in LST preferences.

Symptom-functional states were associated with the likelihood of subsequent membership in the nutrition-preferring state only. Terminally ill cancer patients were significantly more likely to be in the nutrition-preferring state in reference to the comfort-preferring state if they were in the state of moderate symptom distress with severe functional impairment than in the best symptom-functional state in the previous wave of assessment. Worse physical functioning has been shown to predispose terminally ill patients to prefer less aggressive LSTs,[17,21,32] whereas physical symptom distress was not correlated with LST preferences.[32] Our results suggest that physical functioning is more powerful than physical symptom distress in terminally ill cancer patients deciding their LST preferences. We found that participants with severe functional impairment significantly preferred receiving nutrition support rather than rejecting all six LSTs when they had high functioning and mild symptom distress. Nutrition support has been recognized as Taiwanese/Chinese people's prime need (*mín yǐ shí wéi tiān*; food is man's paramount necessity). Receiving food and nutrition at EOL is culturally appropriate and necessary not only to deter physical deterioration but also not to be abandoned as a "starving soul" or "hungry ghost/spirit" in hell.[57] Therefore, when they suffered severe functional impairment but moderate symptom

distress only, terminally ill Taiwanese cancer patients preferred to continuously receive nutrition support but rejected other aggressive LSTs such as CPR, ICU care, and intubation with mechanical ventilation to sustain their life without introducing further intolerable symptom distressing or suffering from aggressive LSTs.

Strengths and Limitations

Our study has several strengths: 1) it comprehensively and longitudinally evaluated factors predisposing LST-preference states over cancer patients' last six months, with a focus on factors amenable to effective management/treatments; 2) lagged time-varying variables were built into our HGLM to establish a clear time sequence in their associations with LST-preference states; and 3) advanced statistical approaches were used to parsimoniously identify LST-preference states, thus facilitating clinical applications and avoiding burdening cancer patients with collecting excessive data when they are dying. However, the study had several limitations. First, our convenience sampling from a single medical center in Taiwan may have compromised the representativeness and generalizability of our findings to the target population. Specifically, our participants were relatively young, few had lung cancer, and a high proportion had accurate prognostic awareness (Table 1), possibly underrepresenting elderly patients with lung cancer whose prognosis was not disclosed or those with little prognostic awareness. Our findings from Taiwan need to be replicated for terminally ill cancer patients in other countries where cultural, societal, and health care characteristics may substantially differ, especially for the nonconsistent roles played by QOL, depressive symptoms, and symptom-functional states in associations with distinct LST-preference states. Second, our investigation into LST-preference states was limited to the six LSTs assessed. Third, we repeatedly and frequently assessed participants' LST preferences over their dying process because the extent to which their EOL-care preferences are honored may be distorted if preferences are measured long before death, a common approach of existing research.[13,18,22] However, this repeated assessment (testing)[58] might have suggested to participants that they could change their perceptions, attitudes, and behaviors. Fourth, because our study was observational, we cannot establish a cause-effect relationship between our identified factors and distinct LST-preference states despite our arrangement of time-varying predictors in a distinct time sequence. Finally, other factors predisposing patients' distinct LST-preference states, including family caregivers' and physicians' attitudes and preferences toward LSTs,[56] were not explored and warrant further investigation.

Conclusion and Clinical Implications

Terminally ill Taiwanese cancer patients' LST preferences remain stable even when death approaches, and their distinct LST-preference states are significantly associated with accurate prognostic awareness, physician-patient EOL-care discussions, QOL, depressive symptoms, and symptom-functional states. Health care professionals should cultivate accurate prognostic awareness and facilitate discussions about goals, values, and preferences for EOL care early in terminally ill cancer patients' dying trajectory to improve their realistic expectations of LST efficacy at EOL, thereby increasing the likelihood of rejecting futile LSTs. Enhancing QOL not only achieves high-quality EOL care for terminally ill cancer patients but may also eliminate their uncertainty in making EOL-care decisions.[56] Adequate psychological support should be provided to terminally ill cancer patients with more depressive symptoms and severe functional impairment to support their preference for rejecting aggressive LSTs (e.g., CPR, ICU care, and mechanical ventilation support) regardless of nutrition-support preference, thus achieving personalized and high-quality EOL care.

Disclosures and Acknowledgments

This study was funded by National Health Research Institutes (NHRI-EX107-10704PI) and Ministry of Science and Technology (MOST 107-2314-B-182-064-MY3) and Chang Gung Memorial Hospital (BMRP888).

The authors declare no financial or other conflict of interest.

No funding sources had any role in designing and conducting the study: collecting, managing, analyzing, and interpreting the data; or preparing, reviewing, or approving the manuscript.

The corresponding author has full access to all study data, analyzed the data with Dr. Fur-Hsing Wen, and takes responsibility for the integrity of the data and accuracy of the data analysis.

Ethical approval: The study site's ethical committee approved the study (98-0476B). All participants signed written informed consent.

References

1. Institute of Medicine. Dying in America: improving quality and honoring individual preferences near the end of life. Washington, DC: The National Academies Press, 2014.

2. Sudore RL, Heyland DK, Lum HD, et al. Outcomes that define successful advance care planning: a Delphi panel consensus. J Pain Symptom Manage 2018;55:245–255.

3. Allison TA, Sudore RL. Disregard of patients' preferences is a medical error: comment on "Failure to engage

hospitalized elderly patients and their families in advance care planning". JAMA Intern Med 2013;173:787.

4. Heyland DK, Barwich D, Pichora D, et al. Failure to engage hospitalized elderly patients and their families in advance care planning. JAMA Intern Med 2013;173:778–787.

5. Peppercorn JM, Smith TJ, Helft PR, et al. American society of clinical oncology statement: toward individualized care for patients with advanced cancer. J Clin Oncol 2011;29:755–760.

6. Tulsky JA, Beach MC, Butow PN, et al. A research agenda for communication between health care professionals and patients living with serious illness. JAMA Intern Med 2017;177:1361–1366.

7. Cox CE, Martinu T, Sathy SJ, et al. Expectations and outcomes of prolonged mechanical ventilation. Crit Care Med 2009;37:2888–2894.

8. Heyland DK, Frank C, Groll D, et al. Understanding cardiopulmonary resuscitation decision making: perspectives of seriously ill hospitalized patients and family members. Chest 2006;130:419–428.

9. Bekelman JE, Halpern SD, Blankart CR, et al. Comparison of site of death, health care utilization, and hospital expenditures for patients dying with cancer in 7 developed countries. JAMA 2016;315:272–283.

10. Smith TJ, Hillner BE. Bending the cost curve in cancer care. N Engl J Med 2011;364:2060–2065.

11. Sullivan R, Peppercorn J, Sikora K, et al. Delivering affordable cancer care in high-income countries. Lancet Oncol 2011;12:933–980.

12. Wright AA, Keating NL, Ayanian JZ, et al. Family perspectives on aggressive cancer care near the end of life. JAMA 2016;315:284–292.

13. Wright AA, Mack JW, Kritek PA, et al. Influence of patients' preferences and treatment site on cancer patients' end-of-life care. Cancer 2010;116:4656–4663.

14. Rose JH, O'Toole EE, Dawson NV, et al. Perspectives, preferences, care practices, and outcomes among older and middle-aged patients with late-stage cancer. J Clin Oncol 2004;22:4907–4917.

15. Fried TR, Bradley EH, Towle VR, Allore H. Understanding the treatment preferences of seriously ill patients. New Engl J Med 2002;346:1061–1066.

16. Barnato AE, Anthony DL, Skinner J, et al. Racial and ethnic differences in preferences for end-of-life treatment. J Gen Inter Med 2009;24:695–701.

17. Maida V, Peck J, Ennis M, Brar N, Maida AR. Preferences for active and aggressive intervention among patients with advanced cancer. BMC Cancer 2010;10:592.

18. Auriemma CL, Nguyen CA, Bronheim R, et al. Stability of end-of-life preferences: a systematic review of the evidence. JAMA Intern Med 2014;174:1085–1092.

19. Janssen DJ, Spruit MA, Schols JM, et al. Predicting changes in preferences for life-sustaining treatment among patients with advanced chronic organ failure. Chest 2012;141:1251–1259.

20. Houben CHM, Spruit MA, Schols JMGA, Wouters EFM, Janssen DJA. Instability of willingness to accept life-sustaining treatments in patients with advanced chronic organ failure during 1 year. Chest 2017;151:1081–1087.

21. Hwang IC, Keam B, Yun YH, Ahn HY, Kim YA. Quality of life changes and intensive care preferences in terminal cancer patients. Palliat Support Care 2015;13:1309–1316.

22. Mack JW, Weeks JC, Wright AA, et al. End-of-life discussions, goal attainment, and distress at the end of life: predictors and outcomes of receipt of care consistent with preferences. J Clin Oncol 2010;28:1203–1208.

23. Weeks JC, Cook EF, O'Day SJ, et al. Relationship between cancer patients' predictions of prognosis and their treatment preferences. JAMA 1998;279:1709–1714.

24. Tang ST, Liu TW, Chow JM, et al. Associations between accurate prognostic understanding and end-of-life care preferences and its correlates among Taiwanese terminally ill cancer patients surveyed in 2011-2012. PsychoOncol 2014;23:780–787.

25. Laakkonen ML, Pitkala KH, Strandberg TE. Older people's reasoning for resuscitation preferences and their role in the decision-making process. Resuscitation 2005;65:165–171.

26. Wright AA, Zhang B, Ray A, et al. Associations between end-of-life discussions, patient mental health, medical care near death, and caregiver bereavement adjustment. JAMA 2008;300:1665–1673.

27. Voogt E, van der Heide A, Rietjens JAC, et al. Attitudes of patients with incurable cancer toward medical treatment in the last phase of life. J Clin Oncol 2005;23:2012–2019.

28. Tang ST, Liu LN, Liu TW, et al. Physician-patient end-of-life care discussions: correlates and associations with end-of-life care preferences of cancer patients: a cross-sectional survey study. Palliat Med 2014;28:1222–1230.

29. Stapleton RD, Nielsen EL, Engelberg RA, Patrick DL, Curtis JR. Association of depression and life-sustaining treatment preferences in patients with COPD. Chest 2005;127:328–334.

30. Reinke LF, Slatore CG, Udris EM, et al. The association of depression and preferences for life-sustaining treatments in veterans with chronic obstructive pulmonary disease. J Pain Symptom Manage 2011;41:402–411.

31. Winter L, Parker B. Current health and preferences for life-prolonging treatments: an application of prospect theory to end-of-life decision making. Soc Sci Med 2007;65:1695–1707.

32. Albert SM, Lunney JR, Ye L, et al. Symptom burden and end-of-life treatment preferences in the very old. J Pain Symptom Manage 2016;52:404–411.

33. Basch E, Deal AM, Kris MG, et al. Symptom monitoring with patient-reported outcomes during routine cancer treatment: a randomized controlled trial. J Clin Oncol 2016;34:557–565.

34. Hart SL, Hoyt MA, Diefenbach M, et al. Meta-analysis of efficacy of interventions for elevated depressive symptoms in adults diagnosed with cancer. J Natl Cancer Inst 2012;104:990–1004.

35. Haun MW, Estel S, Rücker G, et al. Early palliative care for adults with advanced cancer. Cochrane Database Syst Rev 2017;12:CD011129.

36. Tang ST, Wen FH, Hsieh CH, et al. Preferences for life-sustaining treatments and associations with accurate prognostic awareness and depressive symptoms in terminally ill

cancer patients' last year of life. J Pain Symptom Manage 2016;51:41–51.

37. Seow H, Barbera L, Sutradhar R, et al. Trajectory of performance status and symptom scores for patients with cancer during the last six months of life. J Clin Oncol 2011;29:1151–1158.

38. Sutradhar R, Atzema C, Seow H, et al. Is performance status associated with symptom scores? A population-based longitudinal study among cancer outpatients. J Palliat Care 2014;30:99–107.

39. Reese JB, Blackford A, Sussman J, et al. Cancer patients' function, symptoms and supportive care needs: a latent class analysis across cultures. Qual Life Res 2015;24:135–146.

40. Buckner TW, Wang J, DeWalt DA, et al. Patterns of symptoms and functional impairments in children with cancer. Pediatr Blood Cancer 2014;61:1282–1288.

41. Tang ST, Wen FH, Chang WC, et al. Preferences for life-sustaining treatments examined by hidden Markov modeling are mostly stable in terminally ill cancer patients' last 6 months of life. J Pain Symptom Manage 2017;54:628–636.

42. Wen FH, Chen JS, Su PJ, et al. Terminally ill cancer patients' concordance between preferred life-sustaining treatment states in their last 6 months of life and received life-sustaining treatment states in their last month: an observational study. J Pain Symptom Manage 2018;54:509–518.

43. Tang ST, Chang WC, Chen JS, et al. Trajectory and predictors of quality of life during the dying process: roles of perceived sense of burden to others and posttraumatic growth. Support Care Cancer 2014;22:2957–2964.

44. Cohen SR, Mount BM, Tomas JJN, et al. Existential well-being is an important determinant of quality of life. Evidence from the McGill Quality of Life Questionnaire. Cancer 1996;77:576–586.

45. Zigmond AS, Snaith RP. The Hospital Anxiety and Depression Scale. Acta Psychiatr Scan 1983;67:361–370.

46. McCorkle R, Young K. Development of a symptom distress scale. Cancer Nurs 1978;1:373–378.

47. Benoliel JQ, McCorkle R, Young K. Development of a social dependency scale. Res Nurs Health 1980;3:3–10.

48. Wen FH, Chen JS, Chou WC, et al. Distinct patterns of conjoint symptom distress and functional impairment in the last year of life predict terminally ill cancer patients' survival. J Pain Symptom Manage 2018;55:1443–1451.

49. Wen FH, Chen JS, Chou WC, et al. Quality of life and psychological distress are differentially associated with distinct symptom-functional states in terminally ill cancer patients' last year of life. Psycho-Oncol 2018;27:2111–2118.

50. Wen FH, Chen JS, Chou WC, et al. Family caregivers' subjective caregiving burden, quality of life, and depressive symptoms are associated with terminally ill cancer patients' distinct patterns of conjoint symptom distress and functional impairment in their last 6 months of life. J Pain Symptom Manage 2018 https://doi.org/10.1016/j.jpainsymman.2018.09.009. [Epub ahead of print].

51. Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. Clin Epidemiol 1992;45:613–619.

52. Raudenbush SW, Bryk AS. Hierarchical linear models, Second Edition. Thousand Oaks: Sage Publications, 2002.

53. Enzinger AC, Zhang BH, Schrag D, Prigerson HG. Outcomes of prognostic disclosure: associations with prognostic understanding, distress, and relationship with physician among patients with advanced cancer. J Clin Oncol 2015;33:3809–3816.

54. Rubin EB, Buehler AE, Halpern SD. States worse than death among hospitalized patients with serious illnesses. JAMA Intern Med 2016;176:1557–1559.

55. Sudore RL, Schillinger D, Knight SJ, Fried TR. Uncertainty about advance care planning treatment preferences among diverse older adults. J Health Commun 2010;15(Suppl 2):159–171.

56. Barnato AE. Challenges in understanding and respecting patients' preferences. Health Aff 2017;36:1252–1257.

57. Del Río MI, Shand B, Bonati P, et al. Hydration and nutrition at the end of life: a systematic review of emotional impact, perceptions, and decision-making among patients, family, and health care staff. Psycho-Oncol 2012;21:913–921.

58. Campbell DT. Factors relevant to the validity of experiments in social settings. Psychol Bull 1957;54:297–312.

Appendix 1

Interview questions regarding preferences for life-sustaining treatments

At the first interview, before participants offered their preferences regarding cardiopulmonary resuscitation (CPR), they were told, "If your heart were to stop beating and your life were in danger, your healthcare professionals might provide CPR. CPR consists of a combination of electric shocks to the heart, pumping the chest to stimulate the heart, placing a tube through your mouth or nose into your lungs and attaching this tube to a breathing machine to help with breathing, and heart medications given through the veins." Participants were then asked, "If your life was in danger, would you want to receive CPR?"

For life-sustaining treatments, participants were asked, "If you were dying and (1) your heart stopped beating, would you want your chest to be pumped to stimulate the heart to beat? (2) If you were unable to breathe on your own, would you want to be intubated and on a breathing machine? In this situation, a tube would be placed through your mouth or nose into your lungs. This tube would be attached to a breathing machine. During that time, you would have to be continuously on the breathing machine and would be unable to talk and might be sedated.[30] (3) If you need intensive care, would you like to stay in an intensive care unit (ICU)? An ICU is an isolated care unit that heavily uses health technology to provide intensive care and there is more nursing staff to closely monitor you. If you receive care in an ICU, you could only have contact with your family at specific visiting times. (4) If you cannot eat by yourself, would you be willing to be fed by artificial means, such as feeding through a nasogastric tube or receiving nutritional support by injection?"

Appendix 2

Prevalence of Accurate Prognostic Awareness and Physician-patient End-of-life Care Discussions *Versus* Time Proximity to Death

Time Proximity to Death, days	Total Assessments	Accurate Prognostic Awareness		Physician-patient End-of-life Care Discussions	
	n[a]	*n*[a]	%	*n*[a]	%
1–30	316	241	76.3	58	18.4
31–90	636	466	73.3	77	12.1
91–180	581	407	70.1	52	9.0
Total	1533	1114	72.7	187	12.2

[a]Number of assessments made by participants who could provide data. The number of assessments > the number of participants because some were interviewed > once and others could not be interviewed.