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ORIGINAL ARTICLE

A longitudinal study of the role of patient-reported outcomes on survival prediction of palliative cancer inpatients in Taiwan

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Abstract
Goals of work This study explores the significance of patient-reported outcomes for predicting length of survival of palliative cancer patients.
Patients and methods Patients were recruited upon admission to the inpatient palliative care unit. Weekly assessment of 180 terminal cancer patients was carried out throughout their survival time using the Medical Outcome Study 36-Item Short-Form Health Survey, the Taiwanese version of the M.D. Anderson Symptom Inventory (MDASI-T), the Karnofsky Performance Status (KPS), the Brief Pain Inventory, and the Brief Fatigue Inventory. Generalized estimating equations (GEE) were utilized to analyze whether the patient-reported outcomes predicted survival time.
Main results Of all patients, 64 had one assessment, 51 had two, 25 had three, and 40 had four or more assessments, up to a maximum of eight. The univariate analysis showed that gender ($P<0.01$), KPS ($P<0.01$), the physical component summary score ($P=0.02$), the MDASI-T total score ($P<0.01$), composite fatigue severity ($P<0.01$), and composite pain severity ($P<0.01$) were significantly associated with length of survival. The multivariate analysis showed that gender ($P<0.01$), KPS ($P<0.01$), and the MDASI-T total score ($P=0.01$) were significant predictors of survival time.
Conclusions This is the first study to explore the significance of patient-related outcomes for predicting length of survival of palliative cancer patients using the GEE method. This study confirms that overall symptom severity is a significant factor in assessing the length of survival of palliative cancer patients.

Keywords Prognostic factor · Quality of life · Symptom severity · Survival · Palliative patients

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Introduction

Patient-reported experiences are highly valued in palliative care. Patient-reported outcomes (PROs) are defined as "measurement of any aspect of a patient's health status that comes directly from the patient (i.e., without the interpretation of the patient's responses by a physician or anyone else," including disease symptoms, patient functioning, and quality of life (QoL) [61]. In a recent review of the impact of PROs on patient survival after a cancer diagnosis, it was concluded that the most commonly assessed PRO was QoL [19]. Improvement of a patient's QoL is widely agreed to be the ultimate goal of palliative care, making QoL an important end point in palliative care research; however, several recent studies have suggested that QoL may also have an independent prognostic value for assessing the length of survival of terminal patients [44, 56, 57, 67]. The predictive value of QoL for cancer survival has also been noted in descriptive reviews [23, 48, 58]. The World Health Organization's project to develop a quality-of-life measure defines quality of life as "individuals' perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards, and concerns" [59]. Clinical predictions of the length of survival of patients in the end stages of cancer have therapeutic and psychological

implications for the patient and especially for the family [36]. However, accurate survival time estimates for patients with terminal cancer continue to be a challenge for palliative care clinicians.

Some studies have explored the prognostic indicators of length of survival of patients with advanced or terminal cancer [8–10, 19, 46, 49]. To date, several factors have been thought to influence the duration of the terminal phase for cancer patients, but conclusive findings have remained elusive. Identification of such factors could improve prognostic accuracy and facilitate health care providers' decision making in selecting the most appropriate care plan [14]. Prior studies have shown the following to have predictive value for assessing the length of survival of terminal cancer patients: performance status [8–10, 14, 40], pain [40], fatigue [8, 10, 39], clinical symptoms [8, 40], and quality of life [12, 36, 64]. Some studies of cancer patients, including patients not necessarily in a terminal phase, have identified quality of life as having an important prognostic factor [6, 16, 20]. In summary, of the patient-reported outcomes previously identified in the literature, performance status, clinical symptoms, and quality of life are of great value in predicting length of survival of terminal cancer patients. The ability to accurately estimate a patient's length of survival may improve the decision-making process for palliative care and allow patients and their families to better prepare for death.

To determine prognostic factors, most prior studies collected data on only one occasion, compromising results. Moreover, most prior studies focused on individual symptoms, such as pain or fatigue, meaning that the role of overall symptom severity in predicting survival has not been extensively investigated. Therefore, this prospective and longitudinal study aimed to evaluate the significance of overall symptom severity, quality of life, pain, fatigue, and performance status data in survival prediction from a sample of cancer patients admitted to a palliative care unit and collected on a weekly basis throughout their survival time.

Patients and methods

Participants and settings

A longitudinal design was used in this study, which recruited a convenience sample from the palliative care inpatient units at three medical centers in northern Taiwan. Patients were required to meet the following criteria to be included in this study: (1) have a pathological diagnosis of cancer and be admitted to a palliative care unit, (2) be age 18 years or older, and (3) have the ability to communicate in Mandarin or Taiwanese. Patients were not included if they were cognitively impaired (by physicians' judgements), did not want to participate, or could not understand the intent of the study. The final sample consisted of 180 terminal cancer patients enrolled consecutively from the palliative care units. The Institutional Review Boards approved the study.

Instruments

A six-part survey was used to collect data. The survey included the following: (1) the Medical Outcome Study 36-Item Short-Form Health Survey (SF-36), (2) the Taiwanese version of the M.D. Anderson Symptom Inventory (MDASI-T), (3) the Karnofsky Performance Status (KPS), (4) the Brief Pain Inventory-Chinese Version (BPI-C), (5) the Brief Fatigue Inventory-Taiwanese Version (BFI-T), and (6) a demographic questionnaire.

The Medical Outcomes Study Short-Form-36, Taiwanese version

The SF-36 was used to assess quality of life in this study because this generic quality-of-life instrument has been used widely across different disease populations, which provides an opportunity to compare results form this study with other studies or disease populations. The SF-36 has been used in cancer patients [21, 26, 42, 52, 62] and has been examined for its significance in predicting survival in cancer patients [26, 52]. The SF-36 measures health-related quality of life, including physical functioning (ten items); role limitations due to physical health problems (RP, four items); bodily pain (BP, two items); general health (GH, five items); vitality (VT, four items); social functioning (SF, two items); role limitations due to emotional problems (RE, three items); and mental health (MH, five items). A physical component summary (PCS) score was computed by averaging the scores on PF, RP, BP, and GH. A mental component summary (MCS) score was computed by averaging the scores on VT, SF, RE, and MH [66]. The Taiwanese version of SF-36 was validated in a healthy adult sample [38, 60].

The Taiwanese version of the M. D. Anderson Symptom Inventory

The MDASI-T was used to assess multiple symptoms. The original MDASI was developed to measure 13 symptoms in the previous 24-h period of patients with cancer, including symptom intensity and subsequent interference with life activities. The first part of the MDASI consists of 13 single-item measures of symptom intensity, including fatigue, sleep disturbance, pain, drowsiness, poor appetite, nausea, vomiting, shortness of breath, numbness, difficulty remembering, dry mouth, distress, and sadness. Each symptom

item is rated on a scale of 0 (not at all) to 10 (as bad as you can imagine). The second part of the MDASI assesses the extent to which symptoms interfere with the following: general activities, mood, normal work, relations with other people, walking, and enjoyment of life. Each of the six interference items is rated on a scale of 0 (does not interfere) to 10 (completely interferes). A multisymptom severity composite score (an average of the 13 symptom items) and an interference composite score (an average of the six interference items) were computed. The validity and reliability of the MDASI has been established [11].

The MDASI-T was developed using a translation and back-translation process. The MDASI was first translated from English into Taiwanese by a bilingual translator. A second bilingual translator who had not seen the original English version back-translated each item from Taiwanese into English. The back-translated items were compared with the original English items for congruency. This process was repeated until the back-translated items and the original items were in agreement. The MDASI-T has good validity and reliability [35].

Brief Pain Inventory-Chinese version

The BPI-C was used to assess pain intensity and its resulting interference with life activities [47]. Each item on the BPI is rated on a scale of 0 (no pain) to 10 (the worst pain I can imagine). The first part of the BPI consists of the following four single-item measures of pain intensity: (1) worst pain (please rate your pain by circling the number that best describes your pain at its worst in the last 24 h), (2) least pain (please rate your pain by circling the number that best describes your pain at its least in the last 24 h), (3) average pain (please rate your pain by circling the number that best describes your pain on average), and (4) pain now (please rate your pain by circling the number that tells how much pain you have right now). The second part of the BPI consists of seven items (each item again rated on a scale of 0 to 10) which assess the extent of pain interference with the following: general activities, mood, walking, working, relations with others, sleeping, and enjoyment of life. An interference score (the average of the seven items) was computed. The reliability and validity of the BPI have been established [7, 32, 65].

Brief Fatigue Inventory-Taiwanese version

Fatigue was assessed with the BFI-T, which was originally developed at the University of Texas M. D. Anderson Cancer Center to measure fatigue in cancer patients. The BFI uses a scale of 0 to 10 to measure fatigue severity and interference with life activities in the previous 24 h. The first part of the BFI measures worst fatigue during the past 24 h, usual fatigue during past 24 h, and fatigue now, with each item rated from 0 (no fatigue) to 10 (fatigue as bad as you can imagine). A composite fatigue severity score is the average of the three severity items. The second part of the BFI assesses the extent to which fatigue interferes with the following: general activities, mood, walking, normal work, relations with other people, and enjoyment of life. Each of the previous items is rated on a scale of 0 (does not interfere) to 10 (completely interferes). A composite fatigue interference score is the average of the six interference items. The validity and reliability of the BFI has been established [43]. The BFI-T was developed using a translation and back-translation process. The psychometric properties of the BFI-T have been established [34].

Karnofsky Performance Status

The KPS was used to assess patients' performance status. The KPS is rated on a scale of 1–100, in steps of ten and has been documented to have good predictive validity [5].

Questionnaire for demographic and disease information

A demographic information sheet covered basic patient information, including age, gender, education, marital status, religious beliefs, and occupation. A disease information sheet recorded each patient's diagnosis, medications, and treatment status, as well as whether metastasis had occurred.

Procedure

Approval for this study was obtained from the Human Subject Committee of the hospital. The researcher approached patients individually to describe the study and obtain informed consent. Upon admission to the palliative care unit and after their informed consent was obtained, the patients were asked to complete all self-administered questionnaires. The researcher completed the KPS. Assessment with the SF-36, MDASI-T, BFI-C, BFI-T, and KPS was repeated every week for the remainder of the patient's life. The mean (SD) number of evaluations performed was 2.43 (1.56). Specifically, 64 (36%) patients had one assessment, 51 (28%) had two, 25 (14%) had three, and 40 (22%) had four or more assessments, up to a maximum of eight.

Statistical analysis

Data on demographic and disease information and on the KPS, SF-36, MDASI-T, BPI-C, and BPI-T were analyzed by descriptive statistics. To take into account the dependence of repeated measurements, a statistical method called generalized estimating equations (GEE) [30, 31, 68] was applied in this study. The GEE method, an extension of the

quasi-likelihood approach, is being increasingly used to analyze longitudinal and other correlated data, especially when they are binary or in the form of counts [22]. The method of GEE is a generalization of generalized linear model that takes into account this within-group correlation [30, 31, 68]. The GEE method was used in this study to analyze whether survival time was predicted by the KPS, SF-36, MDASI-T, BPI-C, and BPI-T measured weekly. Log transformation was used with survival time in order to achieve a normal distribution. Therefore, survival time with a log transformation serves as an outcome variable in the GEE model. All *P* values were set at 0.05.

Results

Participant and disease-related characteristics

Demographic and disease-related characteristics of patients are presented in Table 1. The participants were diagnosed with various types of cancer, including, but not limited to, lung, colorectal, gastric, liver, and head and neck cancer. Sixty-eight percent of participants were male and 76% were retired. The average age was 67.27 years. The mean survival duration from admission to death was 18.91 days and median survival time was 14 days. Figure 1 shows the global survival curve of the sample, which highlights unequivocally that the study was performed on a group of patients in the terminal phase. The means (SD) of major outcome variables and severity for 13 symptoms in the patients' last 4 weeks of life are summarized in Table 2, showing that all variables were deteriorating for patients toward the end of their lives. The four most severe symptoms experienced by patients in the last week of their lives were fatigue, sleep disturbance, drowsiness, and lack of appetite.

Factors for predicting length of survival of terminal cancer patients

The GEE method was used to analyze predictors of survival time, as well as to control for the baseline heterogeneity and time effects (i.e., changes in outcome variables resulting from the passage of time). After controlling for the baseline heterogeneity and time effects, univariate analysis of survival time (after log transformation) highlighted prognostic significance of several variables and symptoms investigated (Table 3). Gender, KPS, the PCS score, the MDASI-T total score, composite fatigue severity, and composite pain severity were significantly associated with survival time in the univariate analysis. In addition to the MDASI-T total score, most items in the MDASI-T, including pain, fatigue, sleep disturbance, distress, shortness of breath, difficulty remembering, poor appetite, drowsiness, dry mouth, sadness,

Table 1 Demographic and disease-related characteristics (*N*=180)

Characteristics	Mean	SD	Number	Percentage
Age (years)	67.27	13.10		
Education (years)	9.99	4.77		
KPS	22.61	7.05		
Days from admission to death	18.91	16.71		
Sex				
Male			123	68
Female			57	32
Marital status				
Married			128	71
Other			52	29
Religious affiliation				
Buddhist and Taoist			114	63
Christian			28	16
None			22	12
Other			16	9
Retired				
Yes			137	76
No			43	24
Cancer diagnosis				
Lung			39	22
Colorectal			29	16
Gastric			21	12
Liver			19	11
Head and neck			17	10
Pancreatic and bile track			14	8
Breast			8	4
Urology			2	1
Other			30	16
Days from admission to death				
1–7 days			56	31
8–14 days			36	20
15–21 days			32	18
22–30 days			19	11
31–67 days			37	20

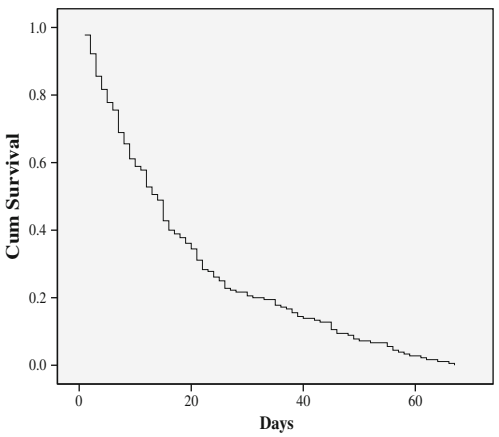

Fig. 1 Overall survival of 180 patients

Table 2 Mean (SD) major outcome variables and severity for 13 symptoms during the 4 weeks prior to death

Weeks before death	<1 week		>1–<2 weeks		>2–<3 weeks		>3–<4 weeks	
	(*n*=180)		(*n*=116)		(*n*=65)		(*n*=40)	
	M	(SD)	M	(SD)	M	(SD)	M	(SD)
KPS	15.33	(6.38)	22.50	(6.17)	24.00	(5.81)	25.00	(5.55)
PCS score	21.06	(3.05)	21.39	(3.21)	21.91	(3.51)	22.09	(3.49)
MCS score	30.05	(6.36)	31.09	(6.71)	31.50	(6.71)	31.20	(7.27)
MDASI-T	7.32	(1.07)	6.86	(1.23)	6.70	(1.40)	6.67	(1.26)
Fatigue severity	8.96	(1.01)	8.19	(1.14)	8.15	(1.20)	8.12	(1.15)
Pain severity	6.26	(1.96)	5.84	(1.76)	5.69	(1.93)	5.58	(1.95)
MDASI-T items								
Pain	7.67	(2.16)	7.07	(2.28)	6.75	(2.49)	6.75	(2.68)
Fatigue	9.23	(1.08)	8.55	(1.03)	8.26	(1.20)	7.90	(1.34)
Nausea	4.69	(3.76)	4.70	(3.64)	4.80	(3.65)	5.03	(3.58)
Sleep disturbance	8.88	(1.24)	8.23	(1.34)	7.89	(1.72)	8.03	(1.72)
Sadness	7.87	(1.61)	7.48	(1.76)	7.43	(1.70)	7.30	(1.79)
Shortness of breath	7.84	(1.99)	7.05	(1.71)	6.83	(2.06)	6.45	(1.81)
Difficulty remembering	7.60	(1.71)	6.96	(1.74)	6.86	(1.88)	6.73	(1.52)
Poor appetite	8.59	(1.79)	7.83	(1.89)	7.65	(2.17)	7.98	(1.29)
Drowsiness	8.74	(1.29)	8.00	(1.43)	7.62	(1.83)	7.78	(1.25)
Dry mouth	7.68	(1.77)	7.27	(1.72)	7.29	(2.15)	7.18	(2.06)
Distress	7.62	(1.55)	7.00	(1.96)	7.08	(1.64)	6.95	(1.81)
Vomiting	2.26	(3.19)	2.77	(3.39)	2.54	(3.22)	2.93	(3.96)
Numbness	6.42	(2.32)	6.22	(2.46)	6.08	(2.25)	5.70	(2.14)

PCS physical component summary, *MCS* mental component summary, *MDASI-T* average of the 13 symptom items, *fatigue severity* average of three severity items, *pain severity* average of four severity items

and numbness were also related with survival time in the univariate analysis (see Table 4).

A multivariate analysis allows one to consider several variables simultaneously and was therefore adopted to evaluate the joint effect of the variables measured at each time point. The variables included in the final model were gender, age, KPS, PCS, MCS, the MDASI-T total score, fatigue composite score, and pain composite score. In the final model, results revealed that gender, KPS, and the MDASI-T total score were significant prognostic indicators of survival time for terminal care patients. Being male, having a lower performance status, and reporting higher levels of overall symptom severity were associated with a shorter length of survival time (Table 5). In other words, overall symptom severity and functional status remain significant prognostic indicators of survival for terminal cancer patients after controlling for demographic variables, quality of life, pain, and fatigue.

Discussion

Patients with terminal cancer and their families frequently request estimations of length of survival in order to plan for

Table 3 Univariate analysis of survival by GEE method (*N*=180)

	β	SE	95% CI		*Z*	*P*
			Lower	Upper		
Gender (control: male)	−0.15	0.05	−0.25	−0.05	9.31	0.00**
Age	0.00	0.00	−0.01	0.00	0.92	0.34
KPS	0.03	0.00	0.02	0.03	180.15	0.00**
PCS	0.02	0.01	0.00	0.03	5.08	0.02*
MCS	0.01	0.00	0.00	0.01	2.89	0.09
MDASI-T	−0.14	0.02	−0.17	−0.11	76.61	0.00**
Composite fatigue severity	−0.13	0.02	−0.17	−0.10	49.37	0.00**
Composite pain severity	−0.05	0.01	−0.06	−0.03	20.65	0.00**

*$P<0.05$; **$P<0.01$

Table 4 Univariate analysis of survival predicted by MDASI-T items by GEE method (N=180)

	β	SE	95% CI		Z	p
			Lower	Upper		
Pain	−0.03	0.01	−0.05	−0.02	15.97	0.00**
Fatigue	−0.14	0.02	−0.17	−0.11	67.71	0.00**
Nausea	0.00	0.00	−0.01	0.01	0.27	0.60
Sleep disturbance	−0.09	0.01	−0.11	−0.06	51.19	0.00**
Distress	−0.05	0.01	−0.08	−0.03	17.67	0.00**
Shortness of breath	−0.07	0.01	−0.09	−0.05	43.78	0.00**
Difficulty remembering	−0.08	0.01	−0.11	−0.06	56.09	0.00**
Poor appetite	−0.07	0.01	−0.09	−0.05	44.09	0.00**
Drowsiness	−0.10	0.01	−0.12	−0.08	85.04	0.00**
Dry mouth	−0.10	0.01	−0.12	−0.08	73.95	0.00**
Sadness	−0.05	0.01	−0.07	−0.04	36.28	0.00**
Vomiting	0.01	0.01	0.00	0.02	3.78	0.05
Numbness	−0.05	0.01	−0.06	−0.03	43.05	0.00**

*P<0.05; **P<0.01

and make the best use of the time that remains [14]. In particular, prediction of survival time often affects the patient's willingness to make use of palliative care programs in the terminal phase [53]. Without the assistance of more precise methods for measuring survival time in terminal cancer patients, health professionals have had to rely on their often inaccurate predictions and studies have documented their tendency to overestimate the length of survival [36, 50, 63]. Therefore, the ability to identify factors that can improve prognostic accuracy is important for health professionals aiding patients and families in their planning and their desire to make the best use of the time remaining.

Since some types of cancer progress rapidly and have poor outcomes, measuring quality of life has become an important end point of clinical trials and studies of cancer care [44], particularly in advanced cancer [2]. The importance of quality of life as a prognostic factor for survival for cancer patients has been studied in recent years on several different cancer populations including brain [41], lung [18, 24, 29, 44, 55], bladder [54], breast [20, 28, 39], esophagus [1, 16], ovary [6], and various terminal cancer sites [36]. Most studies using classical statistical techniques and one-time data reported that global quality of life is a strong prognostic factor for survival in cancer patients [1, 6, 16, 18, 20, 28, 29, 36, 44, 54, 55]. This study, which used a more sophisticated technique and longitudinal data, did not support the importance of quality of life in predicting survival in patients with terminal cancer. Mauer et al. [41] stated that, while classical techniques lead to positive results, more refined analyses suggest that quality-of-life scores add relatively little to clinical factors to predict survival for patients with cancer. The other reason why no association between QoL and time to death was found in this study could be due to the fact that the SF-36 is neither specific for patients with cancer nor for those who are terminally ill [4]. A recent review on the prognostic significance of patient-reported outcomes in cancer clinical trials revealed that the European Organization for Research and Treatment of Cancer Quality-of-Life Questionnaire

Table 5 Multivariate analysis of survival by GEE method (N=180)

	β	SE	95% CI		Z	P
			Lower	Upper		
Gender (control: male)	−0.16	0.05	−0.25	−0.07	12.73	0.00**
Age	0.00	0.00	0.00	0.00	0.00	0.99
KPS	0.02	0.00	0.02	0.02	68.69	0.00**
PCS	0.01	0.01	−0.01	0.02	1.44	0.23
MCS	0.00	0.00	−0.01	0.01	0.07	0.79
MDASI-T	−0.04	0.02	−0.08	−0.01	6.00	0.01*
Fatigue severity	−0.03	0.02	−0.06	0.01	1.63	0.20
Pain severity	0.01	0.01	−0.01	0.03	1.34	0.25

*P<0.05; **P<0.01

C30 or its modules are most commonly used in cancer clinical trials for assessment of quality of life [19]. Moreover, QoL questionnaires assess individuals' subjective health and perception of need satisfaction, which may illustrate a feeling rather than a state of well-being.

Previous studies focusing on predicting survival in advanced or terminal cancer patients have also differed from this study in that they have predominantly examined a specific symptom, such as pain, fatigue, dyspnea, or anorexia. These studies have also generated inconsistent findings [15, 16, 24, 28, 36, 39, 40, 44, 54]. Some studies found that increased pain was predictive of a shorter survival in the multivariate analysis [24, 28, 39]. Other studies, however, found increased pain to be a significant predictor of a shorter survival time in the univariate analysis but not in the multivariate analysis [40]. Most studies found that fatigue was a significant prognostic factor in the univariate analysis but was no longer significant in the multivariate analysis [28, 39, 44, 54]. However, Llobera et al. [36] found that fatigue was an independent predictor of survival both in the univariate analysis and in the final model. Other symptoms demonstrated to be predictive of survival include dysphagia [16], poor appetite [15], anorexia [40, 51], dyspnea [3, 40], and cognitive changes [3, 17].

This study found that overall symptom severity remains a significant prognostic indicator of survival time for terminal cancer patients in the multivariate analysis. The prognostic value of symptom severity is consistent with the results of more limited studies that explored the role of overall symptom severity (i.e., symptom distress) in predicting survival [13, 25]. Degner and Sloan [13] found that patients with advanced cancer reported more distress than those with early-stage disease. Similarly, Kaasa and colleagues found that patients with inoperable small-cell cancer who reported low distress on a four-symptom composite index survived longer than those who reported higher symptom distress. However, these two studies used a cross-sectional design and did not employ multivariate analyses to confirm the role of overall symptom severity in predicting survival.

Moreover, it is interesting to note that male gender was significantly associated with shorter survival in both the univariate and multivariate analyses. The exact reason underlying this phenomenon is unknown; however, it could be because that, in the Taiwanese culture, men tend to assume roles of breadwinners and decision makers in the family. The family members usually want to try their best to prolong a male patient's life. As a result, men may tend to be admitted to the palliative care unit later in their course of cancer illness. Furthermore, there is a higher male prevalence of the sample in this study. This could be because in Taiwan male cancer patients are more likely to receive care in the hospital at the end of life. A recent population-based study in Taiwan revealed that male cancer patients were more likely to die at hospital, while female cancer patients were more likely to die at home [33].

Finally, functional status as measured by KPS was found in both the univariate and multivariate analyses in this study to be a significant predictor of survival. This finding is consistent with previous studies. The KPS has been used as a performance indicator for the last two decades [45] and its association with survival time has been found by many studies. Rosenthal et al. [53] reported that performance status remained the most reliable survival indicator in hospice patients. Loprinzi et al. [37] found that the KPS was capable of distinguishing three populations with statistically different survival time curves in univariate versus multivariate analysis and showing that KPS predictive ability is slightly greater than that of the Eastern Cooperative Oncology Group. In a sample of 304 patients with advanced gastric cancer, Kim et al. [27] found that poor performance status was an independent prognostic factor identified by multivariate analysis. Maltoni et al. [40] reported that multiple regression analysis revealed KPS as an independent predictor of survival time for terminal cancer patients. Performance status remains an important predictor of survival in advanced cancer patients. Studies have shown that performance status is the variable that best predicts survival time for lung cancer patients [29] and advanced breast cancer patients [15]. Moreover, a recent study reported that performance status is a prognostic factor in advanced ovarian cancer for both progression-free survival and overall survival [6].

This study was limited by short follow-up periods, as survival time for patients after admission to a palliative care unit was relatively short. Palliative units in Taiwan appear to admit patients at a later onset of the terminal period than those in some other studies. This could be due to the fact that the philosophy of palliative care has not been widely accepted by all patients, family members, and even health professionals. The mean survival duration from admission to death in this study was 18.91 days and median survival time was 14 days. In a study by Llobera et al. [36], the mean duration from admission to death was 99 days and the median duration of survival was 59 days. In a study by Maltoni et al. [40], the median length of survival was 32 days. The sample in this study thus represents the very terminal phase of cancer and results should therefore be interpreted cautiously. Further research with a longer follow-up period but with a similar design and statistical approach would be useful in exploring the prognostic role of overall symptom severity in terminal cancer patients. Moreover, because the SF-36 is neither specific for patients with cancer nor for those who are terminally ill, the adequacy of the SF-36 in the palliative care setting may

need to be further examined. Lastly, it is desirable to develop and validate a scoring system with appropriate cutoff points for survival prediction for cancer patients at different stages based on this current study and previous studies. Improving the ability to estimate accurately a patient's length of survival may assist in appropriate decisions about treatment modalities and efficient use of treatment resources.

In conclusion, this is the first study to explore the significance of patient-reported outcomes in survival prediction for palliative cancer patients based on information collected weekly until the patient's death and using the GEE method to account for the repeated measurements' dependence. After controlling for other variables shown in previous studies to be prognostic factors for advanced or terminal cancer patients, we found overall symptom severity and functional status to be of predominant importance in predicting survival time for terminal cancer patients. Such prognostic indicators could help clinicians and patients make clinical decisions and tailor treatment. More accurate assessment of survival time could potentially improve communication about treatment options between terminal cancer patients and clinicians and could thus have great potential for improving the quality of palliative care.

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References

1. Blazeby JM, Brookes ST, Alderson D (2001) The prognostic value of quality of life scores during treatment for oesophageal cancer. Gut 49:227–230. doi:10.1136/gut.49.2.227
2. Bottomley A, Flechtner H, Efficace F, Vanvoorden V, Coens C, Therasse P, Velikova G, Blazeby J, Greimel E, European Organisation for Research and Treatment of Cancer (EORTC) Data Center and Quality of Life Group (2005) Health related quality of life outcomes in cancer clinical trials. Eur J Cancer 41:1697–1709. doi:10.1016/j.ejca.2005.05.007
3. Bruera E, Miller MJ, Kuehn N, MacEachern T, Hanson J (1992) Estimate of survival of patients admitted to a palliative care unit: a prospective study. J Pain Symptom Manage 7:82–86. doi:10.1016/0885-3924(92)90118-2
4. Bruley DK (1999) Beyond reliability and validity: analysis of selected quality-of-life instruments for use in palliative care. J Palliat Med 2:299–309. doi:10.1089/jpm.1999.2.299
5. Buccheri G, Ferrigno D, Tamburini M (1996) Karnofsky and ECOG performance status scoring in lung cancer: a prospective, longitudinal study of 536 patients from a single institution. Eur J Cancer 32A:1135–1141. doi:10.1016/0959-8049(95)00664-8
6. Carey MS, Bacon M, Tu D, Butler L, Bezjak A, Stuart GC (2008) The prognostic effects of performance status and quality of life scores on progression-free survival and overall survival in advanced ovarian cancer. Gynecol Oncol 108:100–105. doi:10.1016/j.ygyno.2007.08.088
7. Chang MC, Chang YC, Chiou JF, Tsou TS, Lin CC (2002) Overcoming patient-related barriers to cancer pain management for home care patients: a pilot study. Cancer Nurs 25:470–476. doi:10.1097/00002820-200212000-00012
8. Cheung WY, Barmala N, Zarinehbaf S, Rodin G, Le LW, Zimmermann C (2008) The association of physical and psychological symptom burden with time to death among palliative cancer outpatients. J Pain Symptom Manage. doi:10.1016/j.jpainsymman.2008.03.008
9. Chow E, Harth T, Hruby G, Finkelstein J, Wu J, Danjoux C (2001) How accurate are physicians' clinical predictions of survival and the available prognostic tools in estimating survival times in terminally ill cancer patients? A systematic review. Clin Oncol 13:209–218
10. Chow E, Fung K, Panzarella T, Bezjak A, Danjoux C, Tannock I (2002) A predictive model for survival in metastatic cancer patients attending an outpatient palliative radiotherapy clinic. Int J Radiat Oncol Biol Phys 53:1291–1302. doi:10.1016/S0360-3016(02)02832-8
11. Cleeland CS, Mendoza TR, Wang XS, Chou C, Harle MT, Morrissey M, Engstrom MC (2000) Assessing symptom distress in cancer patients: the M. D. Anderson Symptom Inventory. Cancer 89:1634–1646 doi:10.1002/1097-0142(20001001)89:7<1634::AID-CNCR29>3.0.CO;2-V
12. Coates A, Porzsolt F, Osoba D (1997) Quality of life in oncology practice: prognostic value of EORTC QLQ-C30 scores in patients with advanced malignancy. Eur J Cancer 33:1025–1030. doi:10.1016/S0959-8049(97)00049-X
13. Degner LF, Sloan JA (1995) Symptom distress in newly diagnosed ambulatory cancer patients and as a predictor of survival in lung cancer. J Pain Symptom Manage 10:423–431. doi:10.1016/0885-3924(95)00056-5
14. den Daas N (1995) Estimating length of survival in end-stage cancer: a review of the literature. J Pain Symptom Manage 10:548–555. doi:10.1016/0885-3924(95)00103-6
15. Efficace F, Biganzoli L, Piccart M, Coens C, Van Steen K, Cufer T, Coleman RE, Calvert HA, Gamucci T, Twelves C, Fargeot P, Bottomley A, EORTC-BCG-IDBBC-NDDG (2004) Baseline health-related quality-of-life data as prognostic factors in a phase III multicentre study of women with metastatic breast cancer. Eur J Cancer 40:1021–1030. doi:10.1016/j.ejca.2004.01.014
16. Fang FM, Tsai WL, Chiu HC, Kuo WR, Hsiung CY (2004) Quality of life as a survival predictor for esophageal squamous cell carcinoma treated with radiotherapy. Int J Radiat Oncol Biol Phys 58:1394–1404. doi:10.1016/j.ijrobp.2003.09.100
17. Forster LE, Lynn J (1988) Predicting life span for applicants to inpatient hospice. Arch Intern Med 148:2540–2543. doi:10.1001/archinte.148.12.2540
18. Ganz PA, Lee JJ, Siau J (1991) Quality of life assessment. An independent prognostic variable for survival in lung cancer. Cancer 67:3131–3135 doi:10.1002/1097-0142(19910615)67:12<3131::AID-CNCR2820671232>3.0.CO;2-4
19. Gotay CC, Kawamoto CT, Bottomley A, Efficace F (2008) The prognostic significance of patient-reported outcomes in cancer clinical trials. J Clin Oncol 26:1355–1363. doi:10.1200/JCO.2007.13.3439
20. Gupta D, Granick J, Grutsch JF, Lis CG (2007) The prognostic association of health-related quality of life scores with survival in breast cancer. Support Care Cancer 15:387–393. doi:10.1007/s00520-006-0165-z
21. Gwede CK, Small BJ, Munster PN, Andrykowski MA, Jacobsen PB (2008) Exploring the differential experience of breast cancer treatment-related symptoms: a cluster analytic approach. Support Care Cancer 16:925–933. doi:10.1007/s00520-007-0364-2
22. Hanley JA, Negassa A, Edwardes MD, Forrester JE (2003) Statistical analysis of correlated data using generalized estimating

equations: an orientation. Am J Epidemiol 157:364–375. doi:10.1093/aje/kwf215
23. Hauser CA, Stockler MR, Tattersall MH (2006) Prognostic factors in patients with recently diagnosed incurable cancer: a systematic review. Support Care Cancer 14:999–1011. doi:10.1007/s00520-006-0079-9
24. Herndon JE, Fleishman S, Kornblith AB, Kosty M, Green MR, Holland J (1999) Is quality of life predictive of the survival of patients with advanced nonsmall cell lung carcinoma? Cancer 85:333–340 doi:10.1002/(SICI)1097-0142(19990115)85:2<333::AID-CNCR10>3.0.CO;2-Q
25. Kaasa S, Mastekaasa A, Lund E (1989) Prognostic factors for patients with inoperable non-small cell lung cancer, limited disease. The importance of patients' subjective experience of disease and psychosocial well-being. Radiother Oncol 15:235–242. doi:10.1016/0167-8140(89)90091-1
26. Karvonen-Gutierrez CA, Ronis DL, Fowler KE, Terrell JE, Gruber SB, Duffy SA (2008) Quality of life scores predict survival among patients with head and neck cancer. J Clin Oncol 26:2754–2760. doi:10.1200/JCO.2007.12.9510
27. Kim JG, Ryoo BY, Park YH, Kim BS, Kim TY, Im YH, Kang YK (2008) Prognostic factors for survival of patients with advanced gastric cancer treated with cisplatin-based chemotherapy. Cancer Chemother Pharmacol 61:301–307. doi:10.1007/s00280-007-0476-x
28. Kramer JA, Curran D, Piccart M, de Haes JC, Bruning P, Klijn J, Van Hoorebeeck I, Paridaens R (2000) Identification and interpretation of clinical and quality of life prognostic factors for survival and response to treatment in first-line chemotherapy in advanced breast cancer. Eur J Cancer 36:1498–1506. doi:10.1016/S0959-8049(00)00144-1
29. Langendijk H, Aaronson NK, de Jong JM, ten Velde GP, Muller MJ, Wouters M (2000) The prognostic impact of quality of life assessed with the EORTC QLQ-C30 in inoperable non-small cell lung carcinoma treated with radiotherapy. Radiother Oncol 55:19–25. doi:10.1016/S0167-8140(00)00158-4
30. Liang KY, Zeger SL (1986) Longitudinal data analysis using generalized liner models. Biometrika 73:13–22. doi:10.1093/biomet/73.1.13
31. Liang KY, Zeger SL, Qaqish B (1992) Multivariate regression analyses for categorical data. J R Stat Soc [Ser A] 54:3–40
32. Lin CC (2000) Barriers to the analgesic management of cancer pain: a comparison of attitudes of Taiwanese patients and their family caregivers. Pain 88:7–14. doi:10.1016/S0304-3959(00)00303-1
33. Lin HC, Lin CC (2007) A population-based study on the specific locations of cancer deaths in Taiwan, 1997–2003. Support Care Cancer 15:1333–1339. doi:10.1007/s00520-006-0204-9
34. Lin CC, Chang AP, Chen ML, Cleeland CS, Mendoza TR, Wang XS (2006) Validation of the Taiwanese version of the Brief Fatigue Inventory. J Pain Symptom Manage 32:52–59. doi:10.1016/j.jpainsymman.2005.12.019
35. Lin CC, Chang AP, Cleeland CS, Mendoza TR, Wang XS (2007) Taiwanese version of the M. D. Anderson symptom inventory: symptom assessment in cancer patients. J Pain Symptom Manage 33(2):180–188. doi:10.1016/j.jpainsymman.2006.07.018
36. Llobera J, Esteva M, Rifà J, Benito E, Terrasa J, Rojas C, Pons O, Catalán G, Avellà A (2000) Terminal cancer: duration and prediction of survival time. Eur J Cancer 36:2036–2043. doi:10.1016/S0959-8049(00)00291-4
37. Loprinzi CL, Laurie JA, Wieand HS, Krook JE, Novotny PJ, Kugler JW, Bartel J, Law M, Bateman M, Klatt NE, Dose AM, Etzell PS, Nelimark RA, Mailliard JA, Moertel CG for the North Central Cancer Treatment Group (1994) Prospective evaluation of prognostic variables from patient-completed questionnaires. J Clin Oncol 12:601–607
38. Lu JR, Tseng HM, Tsai YJ (2003) Assessment of health-related quality of life in Taiwan: development and psychometric testing of SF-36 Taiwan version. Taiwan J Public Health 22:501–511 in Chinese
39. Luoma ML, Hakamies-Blomqvist L, Sjöström J, Pluzanska A, Ottoson S, Mouridsen H, Bengtsson NO, Bergh J, Malmström P, Valvere V, Tennvall L, Blomqvist C (2003) Prognostic value of quality of life scores for time to progression (TTP) and overall survival time (OS) in advanced breast cancer. Eur J Cancer 39:1370–1376. doi:10.1016/S0959-8049(02)00775-X
40. Maltoni M, Pirovano M, Scarpi E, Marinari M, Indelli M, Arnoldi E, Gallucci M, Frontini L, Piva L, Amadori D (1995) Prediction of survival of patients terminally ill with cancer. Results of an Italian prospective multicentric study. Cancer 75:2613–2622 doi:10.1002/1097-0142(19950515)75:10<2613::AID-CNCR2820751032>3.0.CO;2-1
41. Mauer ME, Taphoorn MJ, Bottomley A, Coens C, Efficace F, Sanson M, Brandes AA, van der Rijt CC, Bernsen HJ, Frénay M, Tijssen CC, Lacombe D, van den Bent MJ, EORTC Brain Cancer Group (2007) Prognostic value of health-related quality-of-life data in predicting survival in patients with anaplastic oligodendrogliomas, from a phase III EORTC brain cancer group study. J Clin Oncol 25:5731–5737. doi:10.1200/JCO.2007.11.1476
42. McQuellon RP, Russell GB, Shen P, Stewart JH, Saunders W, Levine EA (2008) Survival and health outcomes after cytoreductive surgery with intraperitoneal hyperthermic chemotherapy for disseminated peritoneal cancer of appendiceal origin. Ann Surg Oncol 15:125–133. doi:10.1245/s10434-007-9678-z
43. Mendoza TR, Wang XS, Cleeland CS, Morrissey M, Johnson BA, Wendt JK, Huber SL (1999) The rapid assessment of fatigue severity in cancer patients: use of the Brief Fatigue Inventory. Cancer 85(5):1186–1196 doi:10.1002/(SICI)1097-0142(19990301)85:5<1186::AID-CNCR24>3.0.CO;2-N
44. Montazeri A, Milroy R, Hole D, McEwen J, Gillis CR (2001) Quality of life in lung cancer patients as an important prognostic factor. Lung Cancer 31:233–240. doi:10.1016/S0169-5002(00)00179-3
45. Mor V, Laliberte L, Morris JN, Wiemann M (1984) The Karnofsky performance status scale: an examination of its reliability and validity in a research setting. Cancer 53:2002–2007 doi:10.1002/1097-0142(19840501)53:9<2002::AID-CNCR2820530933>3.0.CO;2-W
46. Morita T, Tsunoda J, Inoue S, Chihara S (1999) The palliative prognostic index: a scoring system for survival prediction of terminally ill cancer patients. Support Care Cancer 7:128–133. doi:10.1007/s005200050242
47. Okuyama T, Wang XS, Akechi T, Mendoza TR, Hosaka T, Cleeland CS, Uchitomi Y (2003) Japanese version of the M. D. Anderson Symptom Inventory: a validation study. J Pain Symptom Manage 26:1093–1104. doi:10.1016/j.jpainsymman.2003.05.003
48. Osoba D (1994) Lessons learned from measuring health-related quality of life in oncology. J Clin Oncol 12:608–616
49. Palmer JL, Fisch MJ (2005) Association between symptom distress and survival in outpatients seen in a palliative care cancer center. J Pain Symptom Manage 29:565–571. doi:10.1016/j.jpainsymman.2004.11.007
50. Parkes CM (1972) Accuracy of predictions of survival in later stages of cancer. BMJ 2:29–31
51. Reuben DB, Mor V, Hiris J (1988) Clinical symptoms and length of survival in patients with terminal cancer. Arch Intern Med 148:1586–1591. doi:10.1001/archinte.148.7.1586
52. Robinson DW, Eisenberg DF, Cella D, Zhao N, de Boer C, DeWitte M (2008) The prognostic significance of patient-reported outcomes in pancreatic cancer cachexia. J Support Oncol 6:283–290

53. Rosenthal MA, Gebski VJ, Kefford RF, Stuart-Harris RC (1993) Prediction of life-expectancy in hospice patients: identification of novel prognostic factors. Palliat Med 7:199–204. doi:10.1177/026921639300700306
54. Roychowdhury DF, Hayden A, Liepa AM (2003) Health-related quality-of-life parameters as independent prognostic factors in advanced or metastatic bladder cancer. J Clin Oncol 21:673–678. doi:10.1200/JCO.2003.04.166
55. Ruckdeschel JC, Piantadosi S (1991) Quality-of-life assessment in lung surgery for bronchogenic carcinoma. Theor Surg 6:201–205
56. Seidman AD, Portenoy R, Yao TJ, Lepore J, Mont EK, Kortmansky J, Onetto N, Ren L, Grechko J, Beltangady M, Usakewicz J, Southrada M, Houston C, McCabe M, Salvaggio R, Thaler H, Norton L (1995) Quality of life in phase II trials: a study of methodology and predictive value in patients with advanced breast cancer treated with paclitaxel plus granulocyte colony-stimulating factor. J Natl Cancer Inst 87:1316–1322. doi:10.1093/jnci/87.17.1316
57. Sloan JA, Loprinzi CL, Laurine JA, Novotny PJ, Vargas-Chanes D, Krook JE, O'Connell MJ, Kugler JW, Tirona MT, Kardinal CG, Wiesenfeld M, Tschetter LK, Hatfield AK, Schaefer PL (2001) A simple stratification factor prognostic for survival in advanced cancer: the good/bad/uncertain index. J Clin Oncol 19:3539–3546
58. Sprangers MA (2002) Quality-of-life assessment in oncology: achievements and challenges. Acta Oncol 41:229–237. doi:10.1080/02841860260088764
59. The WHOQOL Group (1995) The World Health Organization Quality of Life Assessment (WHOQOL): position paper from the World Health Organization. Soc Sci Med 41:1403–1409. doi:10.1016/0277-9536(95)00112-K
60. Tseng HM, Lu JR, Tsai YJ (2003) Assessment of health-related quality of life (II): norming and validation of SF-36 Taiwan version. Taiwan J Public Health 22:512–518 in Chinese
61. United States Food and Drug Administration (2006) Guidance of industry patient-reported outcome measures: use in medical product development to support labeling claims. United States Food and Drug Administration, Rockville
62. van de Poll-Franse LV, Sadetsky N, Kwan L, Litwin MS (2008) Severity of cardiovascular disease and health-related quality of life in men with prostate cancer: a longitudinal analysis from CaPSURE. Qual Life Res 17:845–855. doi:10.1007/s11136-008-9356-z
63. Viganò A, Dorgan M, Bruera E, Suarez-Almazor ME (1999) The relative accuracy of the clinical estimation of the duration of life for patients with end of life cancer. Cancer 86:170–176. doi:10.1002/(SICI)1097-0142(19990701)86:1doi:<doi:170::AID-CNCR23doi:>doi:3.0.CO;2-S
64. Vigano A, Donaldson N, Higginson IJ, Bruera E, Mahmud S, Suarez-Almazor M (2004) Quality of life and survival prediction in terminal cancer patients: a multicenter study. Cancer 101:1090–1098. doi:10.1002/cncr.20472
65. Wang XS, Mendoza TR, Gao SZ, Cleeland CS (1996) The Chinese version of the Brief Pain Inventory (BPI-C): its development and use in a study of cancer pain. Pain 67:407–416. doi:10.1016/0304-3959(96)03147-8
66. Ware JE, Sherbourne CD (1992) The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care 30:473–483. doi:10.1097/00005650-199206000-00002
67. Watson M, Haviland JS, Greer S, Davidson J, Bliss JM (1999) Influence of psychological response on survival in breast cancer: a population-based cohort study. Lancet 354:1331–1336. doi:10.1016/S0140-6736(98)11392-2
68. Zeger SL, Liang KY (1986) Longitudinal data analysis for discrete and continuous outcomes. Biometrics 42:121–130. doi:10.2307/2531248