

# Magnitude of score change for the palliative prognostic index for survival prediction in patients with poor prognostic terminal cancer

Chia-Yen Hung · Hung-Ming Wang · Chen-Yi Kao ·  
Yung-Chang Lin · Jen-Shi Chen · Yu-Shin Hung ·  
Wen-Chi Chou

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## Abstract

**Purpose** The use of the palliative prognostic index (PPI) when used only at an initial assessment might be inappropriate as a prognostic tool because it does not reflect the patient's clinical course. The purpose of this study was to assess the utility of PPI score change ( $\Delta$ score) between two assessments as a prognostic tool in terminally ill cancer patients categorized as having a poor prognosis.

**Methods** A total of 1,035 terminally ill cancer patients categorized as having a poor prognosis (initial PPI score  $>6$ ) under palliative care between January 2006 and December 2011 at a single medical center in Taiwan were selected. Patients were categorized by magnitude of  $\Delta$ score between the initial PPI and week 1 PPI assessments into five groups ( $<-20$ ,  $-20$  to  $0$ ,  $0$  to  $20$ , and  $>20$  %) for survival analysis.

**Results** The median survival was 22 days (range, 8–180 days) in all patients. Median survival duration was 78, 32, 23, 17, and 14 days, and the death rate at the study end was 78.9, 87.1, 96.2, 100, and 100 % in each group, respectively. The c-statistic value for predicting life expectancy less than 30, 60, and 90 days was significantly higher with magnitude of  $\Delta$ score than with the initial PPI score ( $p < 0.05$ ).

**Conclusions** Magnitude of PPI score change within 1-week interval provides a significant difference in survival prediction and is more reliable than initial PPI alone to identify terminally ill cancer patients with better outcome potential in those patients considered to have a poor prognosis.

**Keywords** Palliative prognostic index · Prognostication · Life expectancy · Terminal cancer

## Introduction

Prediction of life expectancy in terminally ill cancer patients is an important issue in end-of-life care, especially for those patients with a poor prognosis [1, 2]. Accurate prognostication of patients with terminal cancer often helps patients in their preparation for dying [3–5], as well as for families to complete patient's final wishes [6], and medical personnel to provide appropriate end-of-life care [7]. However, an over-pessimistic estimate for life expectancy may exacerbate the patient's and family's physical and psychological stress, disrupt the health care provider-patient/family relationship, and may impact treatment planning by medical personnel [8–10].

The palliative prognostic index (PPI) [11] is used worldwide to predict life expectancy in terminally ill cancer patients. The PPI has been validated in various hospice settings with acceptable sensitivity and specificity for end-of-life life expectancy predictions [12–15]. The PPI is scored using five patient clinical features (palliative performance status, dyspnea, oral intake, edema, and delirium). The PPI is considered to be relatively simple and noninvasive, and it does not need the help of subjective clinical personnel for the prediction of survival or additional laboratory examination.

Previously, the PPI was validated as a reliable tool for prognostication in a study that included 623 patients with cancer who were receiving palliative care consultation service (PCCS) in Taiwan [15]. However, the PPI score was over-pessimistic in predicting survival ( $<3$  weeks) and over-optimistic in predicting longer-duration survival. The median survival time was 7 days for patients categorized within poor

C.-Y. Hung · H.-M. Wang · C.-Y. Kao · Y.-C. Lin · J.-S. Chen ·  
Y.-S. Hung · W.-C. Chou (✉)  
Division of Hematology/Oncology, Department of Internal  
Medicine, Chang Gung Memorial Hospital at Linkou, and School of  
Medicine, Chang Gung University, No. 5 Fuxing Street, Guishan  
Township, 333, Taoyuan County, Taiwan  
e-mail: wenchi3992@yahoo.com.tw

prognostic group (PPI score >6) [15]. Among them, 10 % of patients (27 out of 279) remained alive >180 days. Maltoni et al. [14] reported a similar finding in patients with a poor prognosis (PPI score >4)—a median survival of 14 days, and 3.5 % of these patients (13 out of 381) remained alive >180 days. These reports highlight the concern that even the median survival time was accounted by days in patients categorized into the poor prognostic group by PPI; a wide variety of life expectancy existed in this patient group.

A proposed explanation for the discrepancy of predicted survival time is the use of PPI score on the day of patient entry for palliative care; therefore, the estimated prognostication may have been inadequate due to the often unstable condition of the patient and the overlooked influence of subsequent patient condition changes. For example, patients with terminally ill cancer demonstrated a slow decline in functional status over the 6 months before death. In addition, a reduction in performance status, presence of dyspnea, drowsiness, and a lack of appetite, core components of PPI, were increased in the month before death [16]. Considering the dynamic changes observed in patient's clinical features, the utility of the PPI at patient entry to palliative care for prognostication purposes was limited.

The utility of a combination of an initial PPI assessment plus another assessment 1 week post palliative care initiation as a prognostic tool in a 6-year observational cohort with 2,392 terminally ill cancer patients under PCCS was recently evaluated [17]. A significant difference in survival was observed among patients across categories of PPI score change (increase, no change, or decrease) between initial and week 1 PPI assessments. It was concluded that the combination of initial PPI and score change over 1 week is more reliable than an initial PPI alone for prognostication of terminally ill cancer patients undergoing palliative care. In addition to the impact of score change on prognostication, the relationship between the magnitude of score change between two PPI assessments and patient survival has not been addressed in our previous study (17).

We currently hypothesized that the magnitude of score change between two PPI assessments will improve the utility of the PPI scale for prognostication for patients referred to palliative care service, in particular, to identify patients with improved outcomes categorized as having a poor prognosis per PPI score. The aim of the current study was to assess the utility of the magnitude of PPI score change as a prognostic tool in terminally ill cancer patients categorized as having a poor prognosis using PPI score (score >6) at entry of palliative care consultation service.

## Patients and methods

### Patient selection

A total of 4,685 patients with terminal cancer who received care from the PCCS between January 2006 and December

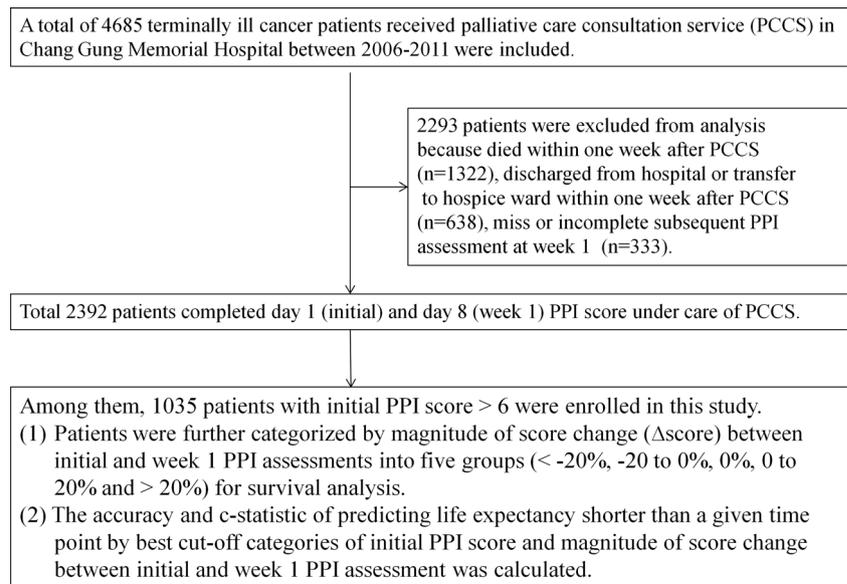
2011 at Chang Gung Memorial Hospital at Linkou, Taiwan, were enrolled consecutively. All the patients had either pathological or radiography-proven malignancies and were referred to PCCS based on their clinicians' judgment that palliative care would be beneficial. Patients were also determined to be unlikely to survive longer than 6 months. A total of 2,392 patients completed PPI assessments at the initial PPI (day 1) and week 1 PPI (day 8). A total of 1,035 out of 2,392 eligible patients who were categorized into the poor prognostic group (PPI score >6) [18] following the initial PPI assessment were selected in this study. Patients were further categorized into five groups, stratified by magnitude of score change ( $\Delta$ score) between the initial and week 1 PPI assessments (<-20, -20 to 0, 0, 0 to 20, and >20 %) for survival analysis. These magnitudes of  $\Delta$ score were selected with the intent of generating preliminary data with a better discrimination of in-group survival. The magnitude of  $\Delta$ score was defined as  $(\text{week 1 PPI score} - \text{initial PPI score}) / (15 - \text{initial PPI score}) \times 100 \%$ . The study flow chart is presented in Fig. 1. The study protocol was approved by the hospital's Institutional Review Board.

### Palliative care consultation service setting

Since 2005, PCCS has provided comprehensive end-of-life care to terminally ill cancer patients through qualified interdisciplinary specialists in an acute ward at Chang Gung Memorial Hospital at Linkou, Taiwan. All participants were under the combined care of a primary care physician and a multidisciplinary palliative care team composed of physicians, specialist nurses, social workers, and a religious specialist. Each patient was interviewed by a physician and nurse specialist at the first consultation and weekly thereafter. Other PCCS team specialists provided care upon request by the physician or nurse specialist. Services were terminated upon patient death, transfer to a hospice ward or home hospice care, or discharge from the hospital under stable condition.

### Data collection

Patient demographics, including age, gender, initial referral source, and the primary cancer were recorded at the first consultation by a specialist nurse using a formulated "patient record form" developed by the Bureau of Health Promotion in Taiwan [19]. The patient record form consisted of Eastern Cooperative Oncology Group performance status (ECOG PS) and 29 additional symptoms, including dyspnea, edema, delirium, appetite, and oral intake amount. A palliative care physician or nurse specialist recorded patients' physical symptoms at each PCCS visit. Patients were considered to have "normal" oral intake if they were receiving total parental nutrition or had an enteral feeding tube. Delirium was diagnosed using the criteria of the Diagnostic and Statistical

**Fig. 1** Study flow chart

Manual of Mental Disorders (Fourth Edition). For patients who had difficulty with verbal communication, a nurse specialist assessed their status using a proxy or caregiver response.

The PPI includes scoring of palliative performance scale (PPS) [20] and four additional clinical variables: oral intake, edema, resting dyspnea, and delirium. PPI sum scores range from 0 to 15 points based on the presence or the absence of the five clinical features. The initial and week 1 PPI score was calculated for each patient using the patient record form. To simplify PPI calculations, the ECOG PS was used instead of the PPS. ECOG PS scores of 0–2, 3, and 4 corresponded to PPS scores of 60–100, 30–50, and 10–20, respectively [21]. Survival time was defined as the day of the initial PPI assessment to the day of death. For outpatients, date of death was obtained from the institutional cancer registration center or the National Register of Death Database in Taiwan. All patients were followed until death or for 180 days from the first day of PCCS referral, whichever came first.

#### Statistical analysis

Basic demographic data were summarized as *n* (%) for categorical variables and medians for continuous variables. The changes in PPI score between the initial and week 1 assessments were calculated using the McNemar's test for binominal variables or the Spearman's correlation test for multinomial variables. Differences in PPI sum scores between the initial and week 1 assessments were analyzed using a paired *t* test. Overall survival was calculated according to the Kaplan-Meier method. Log-rank tests were used to determine significant differences between the survival curves. Hazard ratios (HRs) for PPI sum score subgroups were estimated using multivariate Cox regression adjusted for age, gender,

primary cancer origin, referring medical department, and the interval between the hospital admission and PCCS referral dates. The referring department and interval between the admission and PCCS referral date were adjusted to minimize bias from care received from other sources. Receiver operating characteristic (ROC) curves and the area under the curve (c-statistic) were calculated to determine if the accuracy of life expectancy was shorter than a given time point according to the best cutoff categories of initial PPI score and the magnitude of  $\Delta$ scores. The optimal cutoff categories of initial PPI score and the magnitude of  $\Delta$ scores were selected from ROC curve for calculation of sensitivity, specificity, positive and negative predictive values, and accuracy. Differences in the c-statistic were calculated using MedCalc software, version 12.7.1.0 (MedCalc Software, Ostend, Belgium). Additional statistical analyses were performed using SPSS 17.0 software (SPSS Inc., Chicago, IL, USA). All statistical analyses were considered significant if  $p < 0.05$ .

#### Results

Data from 1,035 patients with terminal cancer were analyzed. The patients' demographic data, origin of primary cancer, referring medical department, and interval between hospital admission and PCCS referral dates are shown in Table 1. Patients had a median age of 60.3 years and were predominantly male (61 %). The most common types of cancer reported by patients were gastrointestinal tract (39 %), thoracic (25 %), and head and neck (12 %). The median time from hospital admission to PCCS referral was 15 days. A majority of patients were referred from the Department of Oncology (52 %).

**Table 1** Baseline patient demographic data ( $n=1,035$ )

Characteristic	<i>n</i> (%)
Age (median)	60.3
<40	96 (9.3)
40–65	526 (50.8)
65–75	204 (19.7)
>75	209 (20.2)
Gender	
Male	634 (61.3)
Female	401 (38.7)
Origin of primary tumor	
Gastrointestinal tract	408 (39.4)
Thoracic	260 (25.1)
Head and neck cancer	128 (12.4)
Genitourinary tract	85 (8.2)
Breast	66 (6.4)
Others	88 (8.5)
Duration from hospital admission to PCCS referral	
<1 week	323 (31.2)
1–2 weeks	191 (18.5)
2–4 weeks	270 (26.1)
>4 weeks	251 (24.3)
Referral department	
Oncology	537 (51.9)
Other medical	333 (32.2)
Surgery	165 (15.9)
Death at end of follow-up	985 (95.2)

The patients' clinical features according to PPI score are summarized in Table 2. The distribution of ECOG PS 0–2, 3, and 4 was 0.5, 22.3, and 77.2 % at the initial PPI evaluation and 2.1, 16.1, and 81.7 % at the week 1 evaluation,

respectively. At the initial and week 1 assessments, patients also reported dyspnea (92.3 and 86 %), delirium (22.2 and 29.2 %), and edema (28.3 and 41.3 %). The distribution of oral intake in normal, reduced but more than a mouthful, and a mouthful or less was 62, 33, 5 and 56.1, 36.5, and 7.3 % of patients at initial and at week 1 PPI, respectively. The initial and week 1 PPI median scores were 8.0 (range 6.5–15, interquartile range 7.5–8.5) and 8.5 (range 0–15, interquartile range 7.5–9.5), respectively. The PPI sum scores and scoring of each PPI clinical variable were significantly increased in severity between the two assessments ( $p<0.001$ ), except dyspnea, which was significantly decreased between the two assessments ( $p<0.001$ ).

The median patient survival was 22.0 days (range 8–180 days). Upon study completion, 985 patients (95.2 %) had died and 50 (4.8 %) remained alive >180 days. The survival time and death rates according to magnitude of  $\Delta$ score are shown in Table 3. Taken together, 10.5 % of patients were assigned to the  $\Delta$ score <–20 % group, 6 % to  $\Delta$ score –20 to 0 % group, 48.8 % to  $\Delta$ score 0 % group, 15.9 % to  $\Delta$ score 0 to 20 % group, and 18.7 % to  $\Delta$ score >20 % group. Death rates for each  $\Delta$ score group (<–20, –20 to 0, 0, 0 to 20, and >20 %, respectively) were 78.9, 87.1, 96.2, 100, and 100 %; median survival time was 78, 32, 23, 17, and 14 days, respectively. The adjusted HR was 0.17 (95 % confidence interval (CI) 0.13–0.23,  $p<0.001$ ), 0.32 (95 % CI 0.24–0.44,  $p<0.001$ ), 0.49 (95 % CI 0.41–0.58,  $p<0.001$ ), 0.83 (95 % CI 0.67–1.03,  $p=0.87$ ) when magnitude of  $\Delta$ score was compared between groups.

The c-statistic for predicting life expectancy less than 30, 60, and 90 days was 0.66 (95 % CI 0.63–0.69), 0.64 (95 % CI 0.60–0.68), and 0.63 (95 % CI 0.59–0.68) for the initial PPI score and 0.72 (95 % CI 0.69–0.74), 0.76 (95 % CI 0.72–0.79), and 0.79 (95 % CI 0.75–0.83) for magnitude of  $\Delta$ score, respectively (Fig. 2 and Table 4). The c-statistic value for

**Table 2** Patient clinical features at the initial and week 1 assessments while under PCCS care ( $n=1,035$ )

Clinical features	Categories	Point of score	Initial PPI (%)	Week 1 PPI (%)	<i>p</i> value
ECOG PS	0–2	0	5 (0.5)	22 (2.1)	<0.001
	3	2.5	231 (22.3)	167 (16.1)	
	4	4	799 (77.2)	846 (81.7)	
Dyspnea	No	0	80 (7.7)	145 (14)	<0.001
	Yes	3.5	955 (92.3)	890 (86)	
Delirium	No	0	805 (77.8)	733 (70.8)	<0.001
	Yes	4	230 (22.2)	302 (29.2)	
Edema	No	0	742 (71.7)	608 (58.7)	<0.001
	Yes	1	293 (28.3)	427 (41.3)	
Oral intake	Normal	0	641 (62)	581 (56.1)	<0.001
	Reduced but more than a mouthful	1	342 (33)	378 (36.5)	
	A mouthful or less	2.5	52 (5)	76 (7.3)	
Median sum score (range, interquartile range)			8 (6.5–15, 7.5–8.5)	8.5 (0–15, 7.5–9.5)	<0.001

**Table 3** Subgroup survival analysis with magnitude of score change for terminally ill cancer patients with initial PPI score >6 ( $n=1,035$ )

Magnitude of score change ( $\Delta$ score)	No. (%)	No. of deaths (%)	Median OS (95 % CI)	Adjusted HR (95 % CI)	<i>p</i> value
<-20 %	109 (10.5)	86 (78.9)	78 (53.8–102.2)	0.17 (0.13–0.23)	<0.001
-20 to 0 %	62 (6.0)	54 (87.1)	32 (27.2–36.8)	0.32 (0.24–0.44)	<0.001
0	505 (48.8)	486 (96.2)	23 (20.9–25.1)	0.49 (0.41–0.58)	<0.001
0 to 20 %	165 (15.9)	165 (100)	17 (15.7–18.3)	0.83 (0.67–1.03)	0.087
>20 %	194 (18.7)	194 (100)	14 (12.9–15.1)	1	
Overall	1,035 (100 %)	985 (95.2)	22 (20.3–23.7)	–	

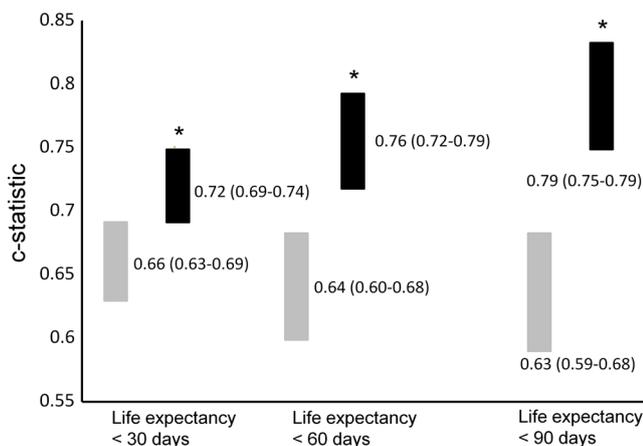
Magnitude of score change=(week 1–initial PPI sum score) / (15–initial PPI sum score) $\times$ 100 %

OS overall survival, HR hazard ratio, CI confidence interval

predicting life expectancy less than 30, 60, and 90 days was significantly different for  $\Delta$ score compared with the initial PPI score ( $p<0.05$ ). The magnitude of  $\Delta$ scores  $\geq 0$  and initial PPI score  $>8$  represented the optimal cutoff value to determinate a life expectancy shorter than a given time point by ROC curve. The accuracy in predicting a life expectancy less than 30, 60, and 90 days was 61.1, 57.1, and 54.9 % when an initial PPI cutoff score  $>8$  was used. When using the magnitude of  $\Delta$ score  $\geq 0$ , the accuracy of predicting a life expectancy less than 30, 60, and 90 days was 71.1, 79.1, and 83.4 %, respectively.

## Discussion

Our study showed that the magnitude of score change between the two PPI assessments provided significant differences in



**Fig. 2** The c-statistic value at the best cutoff point among the categories of initial PPI score (gray rectangle) and magnitude of score change (black rectangle) for predictions of life expectancy less than a given time point. Values inside parentheses represent the 95 % confidence intervals for each c-statistic. Asterisks denote significant differences of c-statistic value for predicting life expectancy at the same time point comparing initial PPI score with magnitude of score change ( $p<0.05$ )

survival prediction in terminally ill cancer patients who were categorized as having a poor prognosis upon initial PPI assessment by a palliative care consultation service. Magnitude of score change was demonstrated to be more accurate than initial PPI alone to identify patients with better outcome potential in those patients considered to have a poor prognosis.

PPI has been commonly used as a prognostic tool for terminally ill cancer patients immediately after enrollment in a palliative care setting [11–15]. The current hypothesis of the PPI prognostic assessment used only at an initial assessment supposes that all patients with terminal disease had a stable clinical course toward death. This assumption was supported by the observation that half of our patients (48.8 %) did not have a change in PPI score ( $\Delta$ score=0) within the 1-week interval between the initial and week 1 follow-up PPI assessment. In the current study, the survival curves were nearly merged in each patient group and subgroups (magnitude of  $\Delta$ score=0). Initial PPI assessment has been demonstrated to be a useful prognosticator for terminally ill cancer patients under PCCS care if patients' clinical features were stable between PPI assessments. However, for patients with an exacerbation of clinical features (34 % of all patients in this study) or improving clinical features (16 % of all patients in this study), a single PPI assessment may not be appropriate as a prognostic tool since it does not reflect subsequent changes in a patient's clinical features.

Utilization of the magnitude of change in PPI score between two time points may offer an improved method to overcome the shortcomings of a single PPI assessment. Downing et al. [16] first reported an association between greater decline in palliative performance scale (PPS) score after palliative care unit admission with a shorter survival probability. Recently, the value of prognostic score changes in terminally ill patients under palliative care has been examined. Seow et al. [22] reported that the rate of transition to death increased fourfold as PPS declined in ambulatory cancer patients. The relative hazard of death increased from 1.045 to

**Table 4** Accuracy of life expectancy shorter than a given time point by best cutoff categories of initial PPI score and categories of magnitude of score change between initial and week 1 PPI assessments

Predicted life expectancy (days)	Best cutoff categories	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
<30	Initial PPI $\geq 8$	58.9	64.8	73.7	48.4	61.1
	$\Delta$ score $\geq 0$	93.5	33.4	70.3	75.4	71.1
<60	Initial PPI $\geq 8$	54.4	69.1	88.6	25.5	57.1
	$\Delta$ score $\geq 0$	41.2	94.2	87.2	46.8	79.1
<90	Initial PPI $\geq 8$	52.9	69.5	92.3	17.6	54.9
	$\Delta$ score $\geq 0$	88.3	49.6	92.4	38	83.4

CI confidence interval, HR hazard ratio, NPV negative predictive value, OS overall survival, PPV positive predictive value

1.69 by adding longitudinal PPS assessments to baseline PPS. Chan et al. [23] reported that the magnitude of PPS change between two time points improved the scale's prognostic usefulness for patients who were referred to palliative care services. Arai et al. [24] reported that the change in PPI per day was an independent factor for predicting life expectancy for cancer patients in a palliative care unit. Our recent study [17] reported that a score change between two PPI assessments was an independent prognostic factor in terminally ill cancer patients under PCCS care regardless of initial PPI score. In the current study, we extended our findings to demonstrate that by using the magnitude of score change, a palliative care specialist could better determine survival among terminally ill patients categorized as having a poor prognosis.

Changes in prognostic scores as part of serial assessments can be used as an independent prognostic factor [16, 17, 23, 24] for patients under palliative care; however, the optimal time interval between the two assessments has not been elucidated. Downing et al. [16] defined a sudden functional decline of  $>10\%$  with the PPS within the first 3 days after initiation of palliative care. Chan et al. [23] calculated the magnitude of PPS change from admission to palliative care to 1-week post-admission. Arai et al. [24] evaluated serial PPI at palliative care initiation and on the fifth to seventh days post-initiation. In our study, the change of PPI scores 1 week post palliative care initiation was used because PCCS was provided to patients on a weekly basis. It is recognized that the change between two assessments in a short period of time (1 week) may not adequately represent a stabilized clinical course; however, evaluating change over a longer period of time may not be practical due to the mortality rate of this patient population. Based on currently available studies, the optimal time interval for prognostication between two assessments is approximately 3 to 7 days [16, 23, 24].

Dyspnea was the only clinical feature to decrease in severity between the two PPI assessments in this study. Dyspnea is one of the most common symptoms in cancer patients under

PCCS in Taiwan with a prevalence of 51–80% [25, 26]. As a core component of PPI, the presence of dyspnea was an important factor in the PPI output. Worth noting, some causes of dyspnea were reversible (such as a correction of anemia or treatment of a lung infection) and a small portion of patients would likely show improvements in PPI scaling and extend life expectancy after medical care.

The strength of this study rests in the prospective observational cohort design, which included a robust patient population over a 6-year period. The major limitations of this study included the use of a single institute and exclusion of patients due to early death or discharge from the hospital before the 1-week PPI assessment; therefore, these results cannot be generalized to all terminally ill cancer patients in Taiwan and worldwide. A multisite, worldwide study is needed to evaluate the role of magnitude of  $\Delta$ score as a prognostic tool for terminally ill cancer patients. Furthermore, PPI intends to assess patient's appetite rather than actual intake. Included patients receiving total parenteral nutrition or enteral feeding tube in normal oral intake category is a potential weakness in this study because the artificial nutrition may carry out without regard to patient's appetite.

## Conclusions

Magnitude of PPI score change between two assessments provides a significant difference in survival prediction and is more reliable than initial PPI alone to identify terminally ill cancer patients with better outcome potential in those patients considered to have a poor prognosis.

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