Palliative Prognostic Index Validation in Hospitalized Advanced Cancer Patients in Indonesia Tertiary Hospitals

Hamzah Shatri,[1,2] Abigail Prasetyaningtyas,[1] Rudi Putranto,[1] Ikhwan Rinaldi[2,3]

[1] Division of Psychosomatic and Pallliative, Department of Internal Medicine, Faculty of Medicine Universitas Indonesia - dr. Cipto Mangunkusumo Hospital, Jakarta, Indonesia.
[2] Clinical Epidemiology Unit, Department of Internal Medicine, Faculty of Medicine Universitas Indonesia – dr. Cipto Mangunkusumo Hospital, Jakarta, Indonesia.
[3] Division of Hematology and Medical Oncology, Department of Internal Medicine, Faculty of Medicine Universitas Indonesia - dr. Cipto Mangunkusumo Hospital, Jakarta, Indonesia.

Corresponding Author:
Hamzah Shatri, MD. Division of Psychosomatic and Palliative, Department of Internal Medicine, Faculty of Medicine Universitas Indonesia – dr. Cipto Mangunkusumo Hospital. Jl. Diponegoro no. 71, Jakarta 10430, Indonesia. Email: hshatri@yahoo.com; psikosomatik@yahoo.com.

ABSTRACT

Background: *Accurate prediction of survival is important for advanced cancer patients such as this to determine medical interventions, to plan the patient's lives and prepare end of life care. The palliative prognostic index (PPI) is most popular scores used worldwide to predict life expectancy in advanced cancer palliative patients. The purpose of this study was to test validity and the performance of PPI in Cipto Mangunkusumo Hospital as a Tertiary Referral Nasional Hospital.* ***Methods:*** *This retrospective cohort study, uses total subject during study with consecutive sampling. Palliative prognostic index was assessed by a palliative care team (PCT). Demographic data were summarized as n (%) and Chi square for categorical variables and median or mean for continuous variables. Overall survival was calculated using the Kaplan-Meier method with hazard ratios. The performance of PPI analyzed using SPSS version 20.0, includes for Receiving Operator Characteristics (ROC) and Hosmer-Lemeshow calibration test.* ***Results:*** *160 patients were included in the PPI study. The subjects have an average age of 50.08 years and are mostly women 68.10%. 28 (17.50%) had symptoms of dyspnoea, 22 (14.60%) pneumonia, and 19 (11.90%) had pain. The number of patients who died during hospitalisation was 83 (51.90%). PPI sum score >6 109 (68,10%). Calibration performance PPI score reached x2 = 8.915 (p = 0.259), and showed correlation r 0.799 (p 0.000). The accuracy of PPI scores in predicting survival in advanced cancer patients in studies for survival <3 weeks 81%, with a sensitivity of 85%, specificity 70%, PPV 86%, and NPV 67%. Predictive accuracy of survival within 3-6 weeks had 76%, sensitivity 66%, specificity 88%, PPV 85% and NPV 70%. PPI score discrimination performance is had a AUC value of 0.822 (95% CI 0.749-0.895).* ***Conclusion:*** *Palliative Prognostic Index (PPI) is valid and has good performance in predicting the survival of advanced cancer patients and may be used to help clinicians in palliative care consultation.*

Keywords*: Cancer, palliative prognostic index (PPI), validation, tertiary hospital.*

INTRODUCTION

Malignancies are increasing globally, especially in developing countries.[1-4] According to the Riskesdas data of 2013[5], the prevalence of cancer patients in Indonesia is 1.4 per 1,000. Of the 240,000 new cases per year, 65% of them seek health assistance at an advanced stage where curative management is no longer effective.[1-5] There are several models created to assist clinicians in predicting prognosis in palliative patients.[6-13] Palliative prognostic index (PPI) is a prognostic score that is popular and commonly used for patients in palliative care units,[14-18] and is recommended by the European Association of Palliative Care.[19]

Palliative prognostic index is a score that has been validated in various medical centres in the word [20-24] was developed in 1999 by Morita[25] et al. in Japan to predict the probability of survival in patients with terminal cancer, by making and summarizing various prognostic factors.

Palliative prognostic index relies on the assessment of five clinical variables which includes performance status using the palliative performance scale, oral intake, absence or presence of dyspnea, edema, and delirium, without requiring blood tests or any clinical prediction of survival.[26-28]

The palliative performance scale is a modification of the Karnofsky Performance Scale Index, which grades a patient's general condition on a scale from 0 (death) to 100 (normal).[29] Palliative performance scale 10-20, 30-50 and >60 with partial score 4, 2.5 and 0. Clinical symptoms of oral intake, divided to mouthfuls or less**,** reduced but more than mouthfuls, and normal with partial score 4, 2.5 and 0. Clinical symptoms of oedema absent or present with partial score 0 or 1, symptoms of dyspnoea at rest absent or present its partial score 0 or 3.5, symptoms of delirium absent or present with partial score 0 or 4. The total PPI score is calculated from the sum of the partial scores of those five variables, range from 0 to 15 points which predicts survival time.[20,24]

The resulting PPI total score puts the patient into one of three groups, predicting survival of more than 6 weeks (PPI score ≤ to 4), 3-6 weeks (PPI score >4-6), or shorter than 3 weeks (PPI score > 6). Palliative prognostic index has been validated in patients with the end stage cancer in a number of settings: hospital, hospice, and home. In different populations there can be differences in the course of the disease, so it is important to assess the prognostic system in the local population. [21,26-28,30,31] Palliative prognostic index has been routinely assessed in advanced cancer patients who have consulted to palliative care team (PCT) at the Cipto Mangunkusumo General Hospital since 2017, but it has not been evaluated yet. The purpose of this study was to test the performance of predicted survival of PPI in hospitalised advanced cancer patients who have consulted to the PCT at Cipto Mangunkusumo Hospital as a tertiary referral Nasional Hospital.

METHODS

This is a retrospective cohort study to assess the performance of the PPI in advanced cancer patients. The sample selection was advanced cancer patients who were consulted to the PCT Cipto Mangunkusumo Referral Hospital from July 2017-December 2018. Palliative prognostic index was assessed by the PCT at first palliative consultation. Secondary data were taken from patients' medical records. The number of samples involved in this study was the total sample who met the inclusion criteria. Sampling technique used is consecutive sampling method from July 2017 to December 2018. Patients who met the inclusion criteria and were not exclude will be followed and the outcome will be observed (died or not) to know the survival. Inclusion criteria includes adult patients over 18 years of age with advanced cancer proven with histopathological examination who are consulted to the PCT. The exclusion criteria in this study includes patients who are in life-support supportive invasive therapy e.g., mechanical ventilation, having unavailable research data and censored patient who are lost to follow up.

Ethics Approval

The study was reviewed and approved by the Institutional Review Board, the Ethics Committee of the Faculty of Medicine of Universitas Indonesia, Cipto Mangunkusumo National Referral Hospital, Jakarta, Indonesia (Ref. Number 235/UN2.F1/ETIK/IPM 00.02/2017).

Statistical Analysis

Statistical analyses were performed using SPSS 20.0 statistics. Basic demographic data were summarized as n (%) and Chi square for categorical variables and median with the interquartile range for continuous variables or mean, respectively. Overall survival was calculated using the Kaplan-Meier method. Hazard ratios were estimated for severe and intermediate PPI sum scores relative to good PPI sum scores (<4) using unstratified Cox regression. The calibration performance of the PPI score system was assessed by the calibration plot and the Hosmer-Lemeshow test. Discrimination performance was assessed by the area under the receiver operating characteristic curve (AUC) which was made based on the predicted mortality of each subject. To investigate the predictive accuracy of prognostic scores, the sensitivity, specificity, positive predictive value, negative predictive value and accuracy of each prognostic score were calculated. Accuracy was calculated by dividing the sum of true positive and true negative cases by the total number. We adopted cut off points according to the original studies. All statistical assessments were considered significant when $p<0.05$.

RESULTS

During the period of July 2017 to December 2018, there were 257 advance stage cancer patients consulted to PCT. Based on the inclusion criteria of the study as well as the availability of medical record data. The number of subjects who were successfully recruited were 160 patients.

The characteristic of the subjects are shown in **Table 1**. Subjects have an average age of 50.08 years, ranging in from 20-83 years. The proportion of women is 68.1%. Data on the clinical characteristics of the subjects showed that the majority knew they had terminal cancer (52.5%). The three main diagnoses at entry were cancer with symptoms of dyspnoea in 28 subjects (17.5%), pneumonia in 22 (14.6%) followed by cancer with symptoms of pain in 19 subjects (11.9%). The number of patients who died during hospitalisation was 83 (51.9%). The time interval between the patient entering and being consulted to the PCT was mostly less than 1 week (63.9%). Patient performance status and clinical symptoms by PPI are summarized in **Table 2**.

Table 1. Patient characteristics.

Patient Characteristics	N (%)
Age (mean, years)	50.08
- ≥60 years	41 (24.30)
- <60 years	119 (70.40)
Gender	
- Female	109 (68.10)
- Male	51 (31.90)
Referral Department	
- Internal Medicine	101 (63.00)
- Onco-Genecology	31 (19.40)
- Surgery	18 (11.03)
- Ear Nose and Throat	5 (3.01)
- Neurology	5 (3.01)
Origin of primary tumour	
- Genecology	43 (26.90)
- Breast	27 (16,90)
- Head and Neck	27 (16.90)
- Digestive	16 (10.00)
- HCC	13 (8.10)
- Lung	11 (6.90)
- Skin and soft tissue	6 (3.80)
- Urology	3 (1.90)
- Bone	3 (1.90)
- Haematology	2 (1.30)
Stage at diagnosis of Cancer	
- Stage IV	84 (52.50)
- Stage III	37 (23.10)
- Stage II	20 (12.50)
- Stage I	7 (4.40)
- No data	12 (7,5)
Reason for Admission	
Symptom's control:	
- Dyspnoea	28 (17.50)
- Pain	19 (11.90)
- Consciousness loss	18 (11.30)
- Appetite loss	17 (10.60)
- Bleeding	6 (3.80)
Pneumonia	22 (14.60)
Anaemia	7 (4.40)
Electrolyte imbalance	6 (3.80)
Gastrointestinal bleeding	4 (2.50)
Diarrheal	3 (1.90)
Sepsis	2 (1.30)
Hospital Outcome	
- In hospital death	83 (51,9)
- Live discharge	77 (48,1)

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- In hospital death	83 (51,9)
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Cause of death	
- Respiratory failure	49 (58.30)
- Multiple organ failure	19 (22.60)
- Sepsis shock	13 (15.80)
- Liver failure	3 (1,9)
Interval from hospital admission to palliative consultation	
- < 1 week	108 (63.90)
- 1 – 2 weeks	30 (17.80)
- >2 – 4 weeks	19 (11.20)
- >4 weeks	3 (1.80)

Table 2. Patient performance status and clinical symptoms base on palliative performance index (PPI)

Clinical Performance	Value	Score	Number (%)
Palliative	≥ 60	0.0	9 (5.6)
Performance	30-50	2.5	84 (52.5)
Scale	10-20	4.0	67 (41.6)
Oral intake	Normal	0.0	83 (51.9)
	Reduced but more than mouthfuls	1.0	45 (28.1)
	Mouthfuls or less	2.5	32 (20)
Oedema	Absent	0.0	87 (44.4)
	Present	1.0	73 (45.6)
Dyspnea at rest	Absent	0.0	81 (51.9)
	Present	3.5	79 (49.1)
Delirium	Absent	0.0	97 (60.90)
	Present	4.0	63 (39.10)

The PPI sum score was ≤ 4 in 30 (18.8%) subjects, 4 - ≤6 in 21 (13.1%) subjects and >6 in 109 (68.1%) subjects.

A Kaplan Meier curve was constructed for each of the groups (Figure 1). The overall median survival was 8 days and for groups 1, 2, and 3 was 68 (47 to 87), 22 (15 to 29), and 5 (3 to 7) days. **Table 3** shows median survival of each category.

From the Kaplan Meier survival curve between the Palliative Prognostic score group and then Cox regression, the value of the PPI Hazard ratio (HR) > 6 was 4.22 (95% CI.2.67-6.66) with a p value of 0.001, and PPI score> 4 and ≤ 6 with the HR 2.02 (95% CI.1.11-3.68) with a p value < 0.02.

The accuracy of PPI score in predicting survivability <3 weeks was 81%, while accuracy in predicting survivability of 3-6 weeks was 76%. Discrimination PPI score expressed by the AUC score was 0.822 (IK95% 0.749-0.895). (**Figure 2**)

The PPI performance in predicting mortality in advanced cancer patients based on the Hosmer-Lemeshow test calibration performance reached x2 = 8.915 (p= 0.259), and showed correlation r 0.799 (p 0.000). (**Figure 3**)

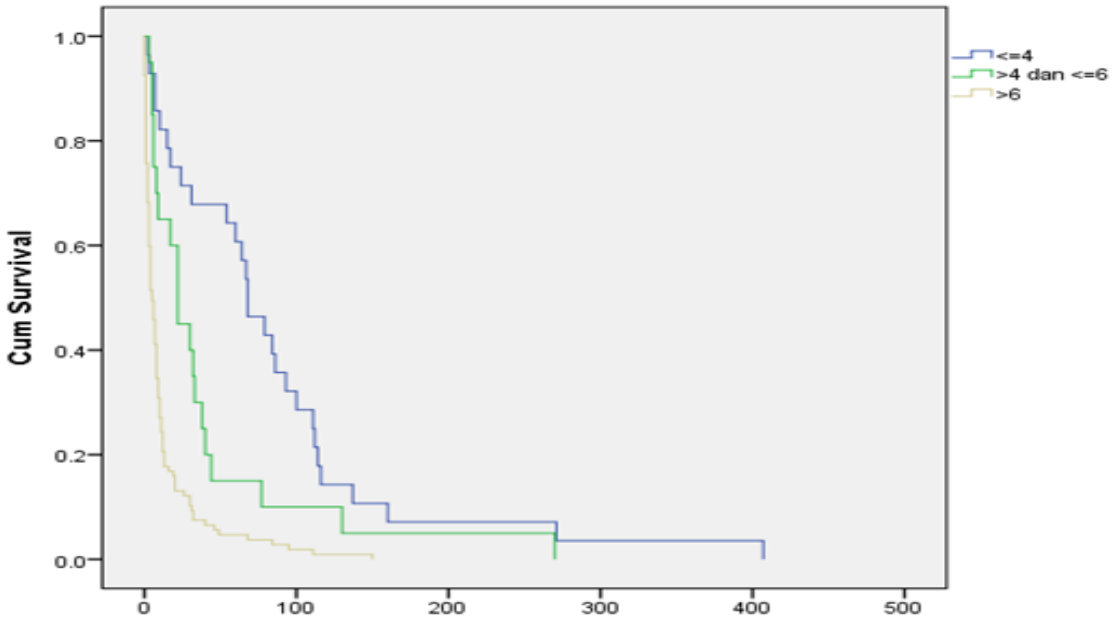

Figure 1. Kaplan-Meier survival curves for each PPI group.

Table 3. Characteristic of the three groups as defined by PPI.

Group	PPI score	N (%)	Median survival Days (95%CI)	HR (95% CI)
1	≤4	30 (18.8%)	68 (46.90-87.09)	reference
2	>4 - ≤ 6	21 (13.1 %)	22 (14.84-29.16)	2.02 (1.11-3.68)*
3	>6	109 (68.1%)	5 (2.98-7.02)	4.22 (2.67-6.66)*
Overall		160 (100%)	8 (6.04-9.95)	

Chi-square analysis of the distribution of survival (Mantel-Cox) *p value of 0.05

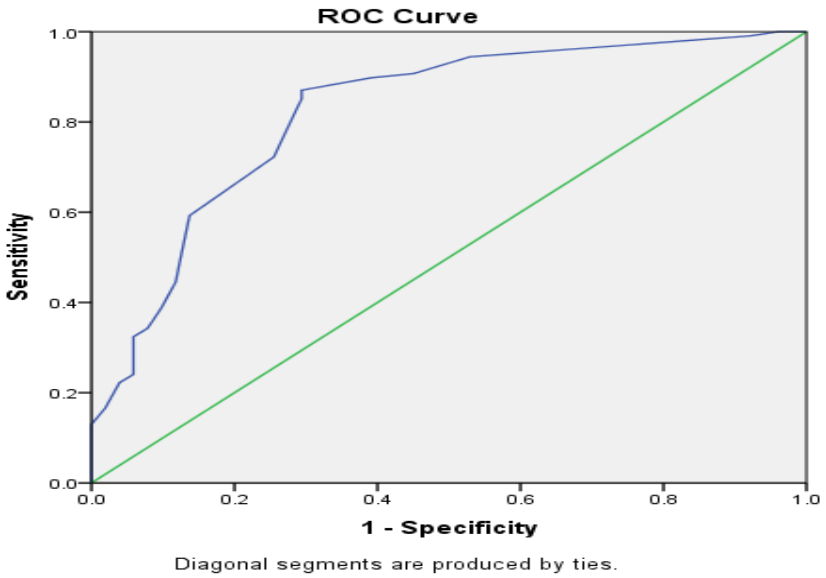

Figure 2. ROC curve of the PPI score.

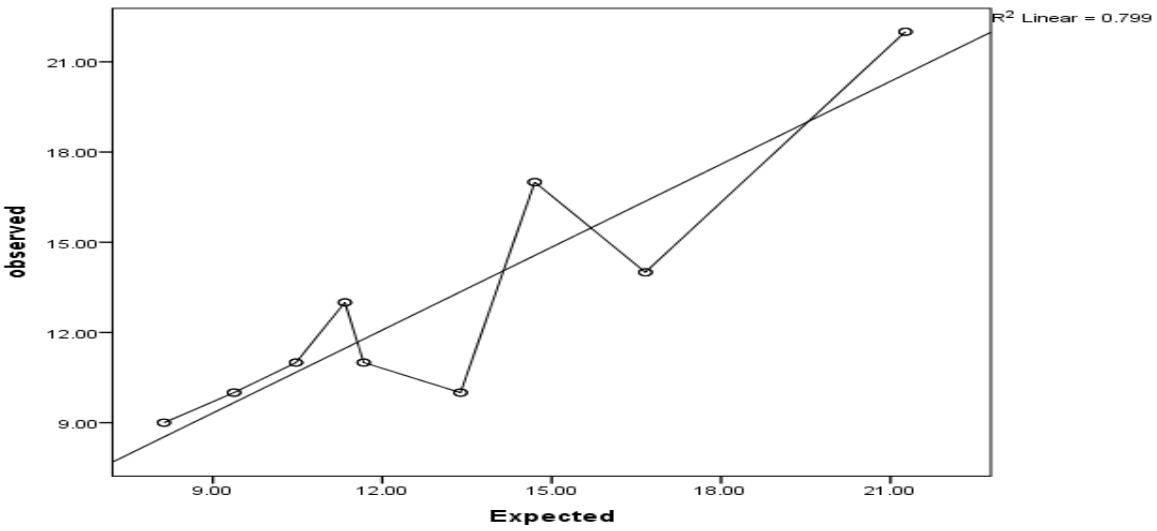

Figure 3. Diagram plot calibrations palliative prognostic index (PPI) scores.

The accuracy of the PPI model in predicting mortality in advanced cancer patients in this study was 81% for survival <3 weeks with a sensitivity of 85%, specificity 70%, PPV 86% and NPV 67%. Accuracy for prediction of survival <6 weeks was 76 %, sensitivity 66% and specificity 88%, with PPV 85% and NPV 70%. (**Table 4**)

Table 4. Accuracy of predictions using PPI

Accuracy	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)	Overall accuracy (%)
<3 Weeks (PPI > 6)	85	70	86	67	81
<6 Weeks (PPI > 4)	66	88	85	70	76

DISCUSSION

Subjects in this study had an average age of 50 years old. The study by Morita et al.[25] in a population of patients with terminal cancer in hospice in Japan had an average age of 66 years old. Meanwhile, Stone et al.[15] found that in cancer patients who received palliative care at the hospital, as well as in hospice and at home in Ireland showed the average age of subjects 69.9 years old. This study had subjects with a younger average age than in other studies. This illustrates the occurrence of cancer in a younger age group in developing countries. This is thought due to the high rates of chronic infection, genetic factors, an increasing number of smokers, especially those who are young, as well as a lack of screening and access to health services.[30]

There were more female subjects than male subjects (68.1% vs 31.9%) which differed from the study of Morita et al.[25] in which there were more men than women. This is because breast cancer and cervical cancer having the highest prevalence in Indonesia, different from Japan and other developed countries where lung and gastric cancers have the highest prevalence.[6,25]

Delirium was found in 39.1% of the study subjects. This is consistent with the research by Bush et al.[31] where the prevalence of delirium in patients in palliative care ranged from 13-14% at admission and 88% in the last week of life. Proportion of subjects with PPS 30-50 were 52.5% and those with PPS 10-20 were 41.6%.[31,32] This study shows that the majority (94.1%) of advanced cancer patients were consulted to a PCT with poor performance status and clinical symptoms which includes delirium, dyspnoea, oedema and mouthfuls with PPI score > 6 (68%) that results shows poor prognosis or short survival.[31-41]

Patients in different PPI groups had significantly different lengths of survival in this study. The results showed in group 1 with PPI score <4, median survival was 68 days, in group 2 with PPI score > 4 - ≤ 6 median survival was 22 days, while in group 3 with PPI score >6, median survival was the shortest with only 5 days. The hazard ratio value obtained from the group with a PPI score> 6 compared to the group with a score of ≤ 4 was 4.22 (95% CI, 2.67 - 6.66) with a p value of 0.001, and a PPI score> 4 and ≤ 6 compared with a group with a score of ≤ 4 of 2.02 (95% CI, 1.11 - 3.68) with a p value of 0.021. Discrimination of the PPI score in the study subjects was expressed by the AUC score of 0.822. A good discrimination performance is if the AUC value above 0.8; if the AUC value is 0.7 and above, then it is still acceptable for a prognostic model, and the performance is considered weak if the AUC value is below 0.7. This study shows good calibration performance of PPI scores with the Hosmer-Lemeshow test showing a value of p > 0.05, which means PPI was well-calibrated. In this study, predictions of survival of less than three weeks using a PPI greater than 6 and of less than 6 weeks using a PPI greater than 4 were accurate, with the accuracy of PPV and NPV almost similar to the others include the original study.[15,20,22,26.]

PPI has been shown to improve the clinical predictions of survival by doctors in palliative care. the European association for palliative care working group on prognosis recommended the use of prognostic tools in combination with the clinical prediction of survival to estimate survival of patients with advanced cancer.[19.]

The Palliative Prognostic Index is easy to use and does not require blood testing. It has been validated in patients with the final stage cancer in a number of settings: hospital, hospice, and home.[20-24] This study has shown that it is valid for use in patients with advanced cancer who were consulted to the PCT in Tertiary Referral Hospital.

The limitations of this study include: having a retrospective study design, so that some bias may have existed in the way in which the data were obtained. This study was conducted at the single centre; however, this is the first study validation of the PPI score in Indonesia in advanced cancer patients receiving palliative care. A prospective study to valid PPI scores for all patient's referral to palliative consultation care should be conducted in the future and conducted with a multi-centre setting. Adding variables of PCT clinical judgment and consideration of acute conditions may increase prognostic performance

CONCLUSION

Palliative Prognostic Index scores is valid and has good performance including adequate accuracy and discrimination in predicting the survival of advanced cancer patients. It's can be used to help clinicians predict survival in advanced cancer patients who were consulted to the palliative care team.

ACKNOWLEDGMENTS

We would like to thank to Universitas Indonesia which gave grant to this study PUTI NKB-0379/UN2.R3.1/HKP.05.00/2019.

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