ORIGINAL ARTICLE

Palliative Prognostic Index as a predictor of mortality among geriatric patients with advanced chronic medical conditions

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ABSTRACT

Introduction: This study is to validate Palliative Prognostic Index (PPI) as a tool for six months prognostication in geriatric patients with advanced chronic medical conditions and to identify other independent prognostic markers of survival.

Methods: This was a prospective and observational study of 108 geriatric patients conducted at Pusat Jantung Hospital Umum Sarawak (PJHUS) Kota Samarahan and Sarawak General Hospital (SGH). The PPI scores were calculated and determined at the time of admission. Mortality is considered as the primary outcome. Sensitivity and specificity analysis were conducted to test the accuracy of PPI. The ideal cut-off value for PPI and other associated markers were determined based on the highest value of Youden Index. Cox regression analysis and survival analysis were applied to test the association between potential markers within six months.

Results: PPI score has a significant association with survival within six months based on univariate and multivariate analyses (p<0.05). Total PPI had a hazard ratio of 1.56 (95% Confidence Interval (95%CI): 1.33,1.57). The study shows PPI reported area under the curve-ROC of 0.945 with p<0.001. PPI score with cut-off value of six reports the highest accuracy in predicting death within six months with sensitivity and specificity of 88.6% and 90.6%, respectively. Total PPI score of >6 with serum albumin level ≤25, the sensitivity and specificity tested were 100.0%.

Conclusion: PPI has the potential to be a useful and significant predictor of mortality within six months in the geriatric population with an advanced chronic medical condition. This study also re-emphasised the strong prognostic role of other markers such as Palliative Performance Scale, Barthel Index, and serum albumin level. This study has identified that hypoalbuminemia cut-off value of 25g/dL analysed against PPI score of >5 revealed extremely high accuracy of prognostication for mortality.

KEYWORDS:
PPI, Geriatric, Palliative, Elderly, Prognostic, Albumin

INTRODUCTION

The average life expectancy at birth of the global population is projected to rise. In 2015, individuals aged ≥60 makeup of 12% of the global population or 901 million people, and this is projected to increase by 22% or 2.1 billion people by 2050.[1] In Malaysia, by 2020, the projection of the population aged ≥65 years could reach 7.1% of the population and the percentage could reach to 14.5% by 2040.[2] Advanced age is known to be one of the independent risk factors for higher mortality.[3-6] Various other studies have also shown that advanced chronic medical diseases are associated with a higher degree of mortality.

In dealing with patients who have poor prognosis, the commonest question being asked by patient and family members are; "How long have I got to live, Doctor?" The unfavourable outcome of the patient's prognosis, poorly trained staff, and difficulty to communicate with patients are among the challenges faced by physicians.[7] Indeed, discussion on this matter can be both intellectually and emotionally challenging. Studies have shown that physicians tend to be inaccurate and overestimate the prognoses of terminally ill patients which can have an impact on the patient's remaining quality of life and further delay admission to hospice or end-of-life care pathways.[8,9] The inaccuracy of projection of life will have a significant impact on the amount of unnecessary investigation and management of the patient which will further increase the financial burden on the health care system.[10]

The Palliative Prognostic Index (PPI), Palliative Prognostic Score (PaP), and Eastern Cooperative Oncology Group Performance Status Scale (ECOG-PS) are among the many prognostic models that have been developed and validated for patients with cancer. Nevertheless, the challenges in predicting the prognoses in advanced chronic medical condition and non-cancer patients remain difficult due to heterogeneity of non-cancer patients and unpredictable course of the disease. Furthermore, the usefulness and reliability of the prognostic models in estimating the survival of <6 months in non-oncological patients have shown poor discriminative power and remain uncertain.[11] However, a study by Nieto et al., has shown that PPI can be a useful tool

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in predicting 6-month survival of patients with advanced medical conditions.[4]

Herein, this study aims to investigate the role of PPI score as a prognostic tool in the geriatric patients with advanced chronic medical conditions. It was crucial to exclude patients with known diagnosis of cancer in the study as the PPI score has been previously validated.[9,12,13] PPI comprises of assessment of Palliative Performance Scale (PPS), oral intake, presence of oedema, dyspnoea at rest and delirium. In the earlier study by Morita et al.[14], the authors reported that PPI scores of >6 had three weeks survival prediction with sensitivity of 80% and specificity of 85% based on the survival of 150 terminally ill cancer patients. Based on that study, patients were classified into three groups, Group A (PPI Score 0.0-4.0), Group B (PPI Score 4.1-6.0), and Group C (PPI Score 6.1-15.0). The PPI score then can be used to predict survival for patients with short survivals (<3 weeks or between 3 and 6 weeks) but an estimation of long-term survival (>6 weeks) in advanced cancer patients is limited.

Several other tools and biological markers have been developed and investigated as prognostic markers. Within the scope of this study, the value of PPS, Barthel Index (BI), and serum albumin level as a prognostic marker of survival will also be investigated. The PPI score uses the PPS, which is a modification of the Karnofsky Performance Scale.[15] The PPS criteria include the extent of disease affecting the level of activities, ambulatory status, level of self-care, oral intake status, and level of consciousness. PPS has been shown to be a reliable prognostic tool and correlates well with median survival time in cancer patients.[15,16] The widely used BI, an ordinal scale to measure the functional level of independence, has also been shown to be associated with the risk of mortality in geriatric patients.[17] Furthermore, many studies have described biological parameters such as albumin as an important biomarker for prognosis.[18,19]

General objectives

To validate PPI as a tool for prognostication in geriatric patients with advanced chronic medical conditions.

Secondary objectives

To validate other independent prognostic markers of survival (PPS, BI, and serum albumin level) in the geriatric patients with advanced chronic medical conditions.

METHODOLOGY

Overview of research design

This study was a prospective and observational study conducted at a 16-bedded Geriatric Unit in Pusat Jantung Hospital Umum Sarawak (PJHUS) Kota Samarahan and the general medical wards at Sarawak General Hospital (SGH). Majority of the geriatric age-group patients would be admitted in SGH for initial assessment and treatment prior to transferal to Geriatric Unit for continuity of care and rehabilitation process. The study period was from early September 2018 till end of October 2019. Participation in this study was strictly voluntary and written informed consent was obtained from the patients or the next of kin. Demographic, epidemiological, and clinical data at the time of enrolment into the study were collected. The PPI scores were calculated and determined at the time of admission based on the sum of PPS, assessment of oral intake obtained directly from the patient or the next of kin, presence of oedema, and delirium. The PPS, BI, and serum albumin were identified on admission. The participants were followed-up throughout their admission in the hospital and mortality is considered as the primary outcome. Patients discharged from the ward had follow-up telephone calls for a total duration of six months from the enrolment into the study.

This study was approved by Malaysian Research Ethics Committee, Ministry of Health Malaysia (research ID NMRR-17-2923-38888).

Inclusion and exclusion criteria

The inpatients selected were above the age of 60 and had been diagnosed with one or more of the advanced chronic medical conditions such as cardiac failure with basal New York Heart Association Functional Class 3-4, respiratory disease with basal dyspnoea of Medical Research Council Class ≥3 or on chronic home oxygen therapy, stage 4-5 chronic renal failure based on KDOQI classification, chronic liver disease with Child-Pugh Score ≥7 and all neurological disease with established cognitive impairment of MMSE ≤30 or established limitation with BI <60 points. The exclusion criteria from this study were the presence of active neoplasm and had previously enrolled in the study.

Sample size determination

The aim of this study was to measure the accuracy of PPI as a predictor of mortality among geriatric patients with advanced chronic medical conditions. Hence, the sample size formula was based on sensitivity and specificity analysis. When the prevalence of mortality is expected at 30%, a minimum sample size of 163 subjects (including minimum 49 subjects died) will be required to achieve a minimum power of 80% (actual power=81.0%) for detecting a change in the percentage value of sensitivity of a screening test from 0.50 to 0.70, based on a target significance level of 0.05 (actual p=0.044).[20]

Statistical method

Descriptive analysis was conducted to present the characteristics of patients and medical conditions. Meanwhile, sensitivity and specificity analysis were conducted to test the accuracy of PPI and other markers in predicting survival and mortality. The ideal cut-off was determined based on the highest value of Youden Index for all the markers. Cox regression analysis and survival analysis were applied to test the association between potential markers and survival between six months. All analyses were conducted using SPSS software (SPSS Inc. Released 2007. SPSS for Windows, Version 16.0. Chicago, SPSS Inc) and diagnostic calculator (2020 MedCalc Software Ltd)

RESULTS

A total of 108 patients were enrolled in this study, 58.3% were male and 41.7% female with a mean age of 72.81 (±8.024). The intended minimum sample size of 163 subjects was not achieved as the study had poor participation due to the

Table I: Demographic and Baseline Characteristic of Participants

		Mean (SD)	n (%)
Age (years)		72.81 (8.024)	
Gender	Male		63 (58.3)
	Female		45 (41.7)
BMI (kg/m^2)		23.14 (4.7)	
fulfil inclusion Criteria	Neurological disease		42 (38.9)
	Respiratory disease		37 (34.3)
	Renal failure		37 (34.3)
	Cardiac failure		14 (13)
	Chronic liver disease		2 (1.9)
Co-morbidity	Hypertension		77 (71.3)
	Anaemia		57 (52.8)
	Diabetes mellitus		49 (45.4)
	Chronic kidney disease		42 (38.9)
	Stroke		33 (30.6)
	COPD		31 (28.7)
	Dyslipidaemia		24 (22.2)
	Ischaemic heart disease		18 (16.7)
	Cardiac failure		17 (15.7)
	Bronchiectasis		13 (12)
	Atrial fibrillation		11 (10.2)
	Pressure ulcer		11 (10.2)
	Pulmonary tuberculosis		7 (6.5)
	Venous thromboembolism		7 (6.5)
	Asthma		4 (3.7)

Note: BMI, Body Mass Index

Table II: Hazard Ratio (95% Confidence Interval) for Potential Markers and Survival Within Six Months

Markers	Crude			Adjusted[a]		
	HR	95%CI	p-value	HR	95%CI	p-value
Total PPI	1.444	1.327, 1.571	<0.001	1.559	1.402, 1.734	<0.001
Palliative Performance Scale	2.519	1.921, 3.304	<0.001	2.975	2.188, 4.045	<0.001
Albumin	0.945	0.909, 0.982	0.004	0.940	0.896, 0.986	0.011
Barthel Index	5.217	2.749, 9.900	<0.001	6.017	2.836, 12.768	<0.001

[a]Statistics were calculated using multivariate analysis to control for gender, age, and diagnosis in the analysis.
Note: PPI, Palliative Prognostic Index

Table III: Area under curve-ROC for Potential Markers and the Accuracy to Predict Survival Within Six Months and Mortality

Markers	AUC	95% CI		Cut-off	Sensitivity	Specificity
Predict survived						
Barthel Index	0.772	0.678	0.866	60	0.859	0.682
Albumin levels	0.665	0.561	0.769	29.5	0.803	0.455
Palliative Performance Scale	0.861	0.787	0.934	50	0.886	0.766
Predict died						
PPI	0.945	0.904	0.985	6	0.886	0.906

Note:
All results were statistically significant, p<0.05

Table IV: Accuracy of Palliative Prognostic Index (PPI) on Selected Cut-off of Albumin

Albumin	PPI	Diagnostic accuracy	Value (95%, CI)
ALL	>5	Sensitivity	88.6% (75.4%, 96.2%)
		Specificity	90.2% (79.8%, 96.3%)
		PPV	86.7% (75.1%, 93.3%)
		NPV	91.7% (82.8%, 96.2%)
≤25 g/dL	>5	Sensitivity	100.0% (69.2%, 100.0%)
		Specificity	100.0% (47.8%, 100.0%)
		PPV	100.0%
		NPV	100.0%

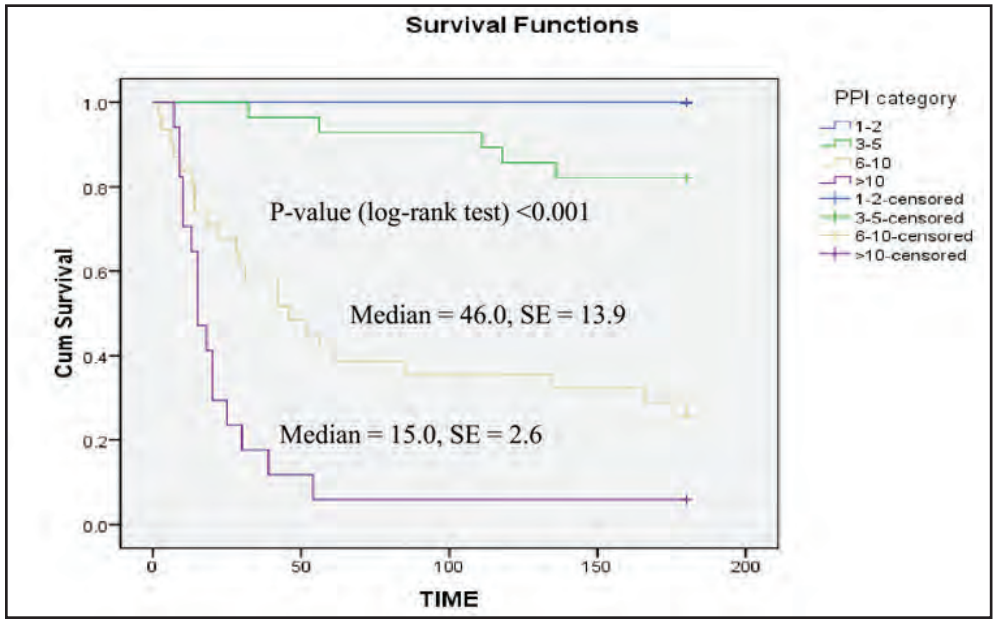

Fig. 1: Palliative Prognostic Index (PPI) categories and magnitude of survival

sensitive nature of the study that dealt with the trajectory of life. Moreover, in this study, a total of nine patients were excluded as they did not fulfil the inclusion criteria and had loss of follow-up upon discharge. Table I shows the demographic and baseline characteristic of the participants. In this study, the most frequent inclusion criteria were neurological disease (42 patients, 38.9%), followed by respiratory disease (37 patients, 34.3%), renal failure (37 patients, 34.3%), cardiac failure (14 patients, 13%), and chronic liver disease (two patients, 1.9%). The predominant neurological disease encountered in this study was mainly stroke. There were 24 patients included in this study that had more than one inclusion criteria fulfilled.

PPI score and the other three markers (PPS, BI, and serum albumin level) were selected and tested to determine their association with survival within 6 months. In Table II, this study has identified that all four markers have an association with survival within 6 months based on univariate and multivariate analyses ($p<0.05$). Total PPI, PPS, and albumin had hazard ratio of 1.56 (95% Confidence Interval (95%CI): 1.33, 1.57), 2.98 (95%CI: 2.19, 4.05), and 0.94 (95%CI: 0.90, 0.99), respectively. BI has the highest hazard ratio of 6.02 (95%CI 2.84, 12.77) in multivariate analysis. As expected, albumin had reversed association with survival within six months (Table II). In this study, the accuracy of potential markers was assessed using Receiver Operating Characteristics (ROC) analysis to determine the optimal cut-off based on Youden Index. The study shows PPI reported area under curve-ROC of 0.945 with p-value of <0.001. PPI has the highest accuracy followed by PPS, BI, albumin and the optimal cut-off is presented in Table III. PPI and other markers have the potential to predict the status of survival (survived or died) within six months.

PPI is initially intended to be used to predict survival in terminally ill cancer patients for a period of <6 weeks but here the authors have identified that PPI with cut-off value of six reports the highest accuracy to predict death within six months with sensitivity and specificity of 88.6% and 90.6%, respectively (Table III). Other markers such as BI has a cut-off of 60 (sensitivity 85.9%, specificity 68.2%) and serum albumin cut-off value at 29.50 (sensitivity 80.3% and specificity 45.5%) to predict survival. In this study, PPS cut-off value 50 has the ability to predict survival with sensitivity and specificity of 88.6% and 76.6%, respectively.

The PPI scores were further categorised into four groups (PPI Score 1-2, 3-5, 6-10, and >10). In Figure 1, the selected categories show a significant difference in the magnitude of survival and good discriminatory power, whereby PPI score >5 can be considered as higher risk of mortality compared with the lower PPI score categories (Categories 1-2 and 3-4). Further analysis was carried out to assess the accuracy of PPI in predicting survival within six months based on selected cut-off for albumin. When the PPI is >5 and albumin ≤25, the sensitivity and specificity were 100.0% (Table IV). For PPI score >5 irrespective of the value of albumin, the sensitivity and specificity remain high at 88.6% (95%CI: 75.4%, 96.2%) and 90.2% (95%CI: 79.8%, 96.3%), respectively.

DISCUSSION

This study shows that PPI taken on admission is a useful, significant, and can potentially be an important tool to predict mortality within six months period. PPI had been numerously validated as a predictive model for mortality in patient with underlying cancer.[9,12,13] Nevertheless, studies which look into PPI as a prognostic tool in non-cancer patients are limited. In Table II, the total PPI score has a

hazard ratio of 1.559 (p<0.001) and Table IV indicates that PPI score of >5 had a good sensitivity (88.6%) and specificity (90.6%). Morita et al., initially reported that prediction of 3-week survival in terminally ill cancer patients was made with a sensitivity of 80% and specificity of 85% using PPI cut-off value >6.[14] Further analysis using Kaplan-Meier plot indicates that PPI strongly correlates with mortality risk as can be seen in Figure 1 which shows the categories with the PPI score of 6-10 and >10 are associated with median mortality of 46 days and 15 days, respectively. Therefore, PPI assessment is a useful screening tool to predict mortality among the geriatric patients with advanced chronic medical conditions. A multicentre prospective and observational study done by Nieto et al also concluded that PPI can be a useful tool in predicting 6-month survival of patients with advanced medical conditions.[4]

Anderson and Downing had introduced PPS, which was later incorporated in PPI and had been shown to be a very important clinical assessment in palliative care and predictor of survivor.[15] The reliability and validity of PPS are proven in a clinical performance assessment tool for palliative care patient.[16] This study has shown that PPS cut-off score of 50 has a sensitivity of 88.6% and specificity of 76.6% to predict survival within the 6-month study period (Table III). This cut-off value of 50 reflects the overall functional performance of patient in ambulation, level of activity, self-care, oral intake, and their level of consciousness.

Matzen et al., reported that BI is a strong independent predictor of survival in older patients who were admitted to the acute geriatric unit.[21] The hazard ratio of BI for survival within 6 months in the study was 6.017 (p<0.001) and based on Table III, the cut-off value for BI was 60, having 85.9% sensitivity and 68.8% specificity. In a Danish nationwide population-based cohort study, it was also evident that BI at admission was strongly and independently associated with mortality in geriatric patients.[17] Similar pattern can be seen in the study when analysing both BI and PPS as predictors of six months mortality among the geriatric patients with advanced chronic medical conditions.

This study reinforces the importance of serum albumin level as an independent prognostic marker of survival using multivariate analysis with a hazard ratio of 0.940 (p=0.011). Albumin cut-off value was 29.5 for prediction of 6-month survival with 80.3% sensitivity and 45.5% specificity. Serum albumin level is associated with 30-day all-cause mortality in acutely admitted medical patient and has an acceptable discriminatory power and good calibration.[22] In a meta-analysis conducted on 90 cohort studies with 291,433 patients by Vincent et al., revealed that for each 10g/L decline in the serum albumin concentration could significantly increase the odds of mortality by 137% and morbidity by 89%, prolonged intensive care unit and hospital stay by 28% and 71%, respectively.[22]

Moreover, the authors have identified that serum albumin level of <25 g/dL with a PPI score of >5, the sensitivity, specificity, positive predictive value, and negative predictive values have shown a diagnostic accuracy of 100%. No other studies at the time of this research had looked into the relation of hypoalbuminemia with a high PPI index as a tool to prognosticate patient survival in both cancer and non-cancerous condition. Whether incorporation of serum albumin level with the PPI score could potentially be a better prognostication tool is yet to be explored. Knowing that low serum albumin could potentially be reversible, could intervention potentially reduce the risk of mortality especially in the setting of high PPI?

LIMITATION

The study sample size did not achieve the desired planned sample size (n=163 subjects) due to the sensitive nature of the study that dealt with trajectory of life. Initially, the sample size planning was calculated based on a prevalence of 30.0% and to detect a change in sensitivity from 0.50 to 0.70. Since this study had achieved more than 80% sensitivity and therefore the sample size of 108 is sufficient to get significant results. The authors have recalculated the sample size to detect a change of sensitivity from 0.50 to 0.80 based on a prevalence of 30%. The study only requires a minimum sample size of 67 subjects with at least 20 mortalities.[20]

CONCLUSION

This study indicates that PPI taken on admission has the potential to be a useful and significant predictor of mortality within six months in the geriatric population with an advanced chronic medical condition. Furthermore, this study emphasised the strong prognostic role of functional status such as PPS, BI and hypoalbuminemia. All these findings could prove to be a useful adjunct in clinical decision making and discussion with patients' family in determining the trajectory of a patient condition. Based on the sample of the study population, the authors have identified that hypoalbuminemia cut-off value of 25 g/dL analysed against PPI score of >5 revealed extreme high accuracy of prognostication for survival. More research is needed to verify this association between low albumin and high PPI score in the future.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

ETHICAL APPROVAL

This study was approved by Malaysian Research Ethics Committee, Ministry of Health Malaysia (research ID NMRR-17-2923-38888 (IIR).

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