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ORIGINAL ARTICLE

Prognostic evaluation in palliative care: final results from a prospective cohort study

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Abstract

Prognostic characterization in the initial assessment of patients with advanced cancer disease is an essential step to plan the most appropriate therapeutic program. Since clinical prediction of survival (CPS) may be of limited value, some authors have tried to integrate specific prognostic factors into prognostic multidimensional scores. We carried out a prospective cohort study in two palliative care units to compare the accuracy of the Palliative Prognostic (PaP) Score, the Objective Prognostic Score (OPS), and the Palliative Prognostic Index (PPI). In addition, we compared the accuracy of the CPS independently estimated by different healthcare professionals and we tested the role of laboratory results, together with clinical and social factors in predicting survival. Clinical and laboratory data of 334 advanced cancer patients were prospectively collected from the time of in-hospital admission. PaP Score was the most accurate index of survival prediction, followed by PPI; CPS estimates' accuracy was similar among physicians and nurse. All healthcare professionals tended to underestimate the real survival. Integrating CPS with multidimensional indexes may further improve the patient's management. The degree of autonomy and the number of metastatic sites were independent prognostic factors for 30-days mortality and overall survival in multivariate analysis.

Keywords Clinical prediction of survival · Palliative care · Prognostic score · PaP Score

Introduction

Most oncologists recognize that the communication of prognosis to cancer patients and their relatives is a fundamental part of the patient-physician relationship [1] and improving this ability remains of great importance within the overall treatment course. In fact, while predicting survival for terminally ill cancer patients is a prerequisite for optimal decision-making, study proposal, and appropriate health service planning, it is often inaccurate [2, 3].

Although subjective and of limited reproducibility, clinical prediction of survival (CPS) is considered one of the best tools to predict patients' outcome. Published data demonstrated that CPS was more accurate in patients with poorer performance status (PS) compared to those fit, and that a stronger doctor-patient relationship is associated with lower prognostic accuracy [4–6].

A systematic review of eight studies that covered more than 1500 professional survival predictions for terminally ill cancer patients showed that these predictions were often inaccurate and dramatically optimistic, because of physicians' attempt to maintain hope [7–9] or unrealistic confidence in novel treatments [10].

The results of this study were partially presented at the 2015 MASCC Annual Meeting, Copenaghen, Denmark.

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Another study that included patients with advanced cancer found that younger patients' age was associated with less accurate survival forecasts [11].

Many recent studies help clinicians identifying clinical predictors for the survival estimation in advanced cancer patients, including cancer anorexia [12] or different biochemical parameters [13, 14].

While a web-based program (Prognostat) provides the historical rates of survival based on clinical parameters [15], the combination of CPS with PS, symptoms and biochemical parameters may help increase the accuracy in clinical practice [16, 17].

Some authors have tried to integrate specific prognostic factors into prognostic multidimensional scores with the aim of providing clinicians with practice tools [18, 19].

PaP Score, originally built for palliative care and validated in a wide range of cancer and non-cancer patient population in different disease stage and setting [20, 21], subdivides patients into three specific risk classes based on six predictive factors for death: dyspnea (0–1), anorexia (0–1.5), PS (0–2.5), CPS (0–8.5), white blood cell count (WBC 0–1.5) and lymphocyte percentage (0–2.5). A numerical score is given to each variable and the overall score derives from the sum of the single scores and it can range from 0 to 17.5. Based on their overall score, patients are included in one of three prognostic groups (score ≤ 5.5; score 5.6–11.0; or score > 11), with a 30-day survival probability of $> 70\%$, 30–70%, or less than 30%, respectively [18].

PPI relies on five clinical parameters that are independently predictors of survival (patient's functional status, oral intake, presence of edema, dyspnea at rest, and delirium). The functional status is measured using the Palliative Performance Scale (PPS), which is a modified Karnofsky Performance Status (KPS), specifically intended for measurement of physical status in palliative care [22, 23].

The total PPI is calculated summing the partial scores (range 0–15) and classifies patients in three groups with survival estimates over 6 weeks, between 3 and 6 weeks and under 3 weeks [24, 25].

This score was validated in hospital palliative care teams, home palliative care services, and acute care hospitals [26].

The OPS is based on the presence of 7 parameters: clinical (anorexia, dyspnea at rest, KPS) and lab test (WBC, bilirubin, creatinine, and LDH values) and was also validated for advanced cancer patients. The total score derived from the sum of single scores and it divides patients in two categories with survival's prevision of 49± 8.3 days and 14± 1.6 days [27, 28].

Few studies directly compared different prognostic tools, and which prognostic model should be preferred in the clinical practice is currently uncertain [19, 20, 29, 30].

The primary objective of the study was to assess the accuracy of Palliative Prognostic (PaP) Score, Objective Prognostic Score (OPS), and Palliative Prognostic Index (PPI) in predicting 30-day survival in terminally ill cancer patients.

In addition, the study aimed to verify the accuracy of CPS in predicting patients' 30-day survival, to evaluate the agreement between two differently experienced oncologists and one nurse in the prognosis estimate and between the estimated and real/actual survival and to test the role of laboratory results, together with clinical and social factors in predicting survival.

Materials and methods

We conducted a prospective cohort study in two distinct palliative care units, the "Area Cure Palliative" in the University and General Hospital of Udine and the Hospice "Casa dei Gelsi" of Treviso, Italy. Clinical and laboratory data of 334 advanced cancer patients were collected at the time of admission (from April 2011 to August 2014).

Data were obtained from medical records according to strict privacy standards.

Inclusion criteria were advanced disease; lack of indications for any oncological treatment, surgery, or radiotherapy; estimated life expectancy of less than 3 months; and KPS between 10 and 50%.

Among other clinical factors, we evaluated patients' activity of daily living (ADL): the range of the final score varies between 0 (complete dependence) and 6 (complete autonomy), based on these six items: bathing, dressing, toilet, physical ambulation, continence, and feeding. We evaluated also the presence of pain (NRS scale—range 0–10), anxiety and/or delirium, and the need for oxygen supplementation. We considered the degree of family in-hospital support (poor-good-very good). Among serological tests, we considered baseline albumin, classified in three categories (< 15 mg/L, 15–25 mg/L, and > 25 mg/L), and reactive C protein (CRP) plasma values. Each member of the study team, composed by a nurse and two physicians, formulated CPS estimation within 48 h of admission. CPS estimates were obtained using closed categories: prevision of survival 1–2 weeks or 3–4 weeks or 5–6 weeks or 7–10 weeks or 11–12 weeks or over 12 weeks.

Blood tests were done within 48 h of hospital admission; if is not possible to obtain blood samples, we examined data from the most recent samples (usually within 2 weeks before admission).

Then, PaP Score, OPS ,and PPI were calculated for each patient. Physician 1 was the senior physician with at least 3 years of experience in palliative care and physician 2 was a trainee in medical oncology; each operator reported his age. Local Investigational Review Boards approved the study.

Statistical considerations

Survival estimates were calculated using Kaplan-Meier method; the accuracy of a 30-day survival prevision by three scores and of CPS were evaluated by ROC curves analysis (the area under the curve, AUC, ranges between 0.5 and 1.0).

Prognostic factors associated with overall survival are studied by a Cox model; the agreement between the CPS expressed by operators and overall survival was assessed by Cohen's k index. k values are classified as it follows: $k \leq 0.2$ "poor agreement," $0.21 < k \leq 0.4$ "weak agreement," $0.41 < k \leq 0.6$ "modest agreement," $0.61 < k \leq 0.80$ "good agreement," $0.81 < k < 1.00$ "very good agreement."

The multiple pairwise comparisons were made by Wilcoxon's test applying Bonferroni correction. Bonferroni correction was obtained dividing the original α-value by the number of comparisons.

The sample size was calculated accepting AUC 0.70 (null hypothesis) as the lower level and as the expected level of accuracy (alternative hypothesis) an AUC value of 0.80. With an alpha error of 5% and a statistical power of 80%, the sample size calculated was 406 patients, 203 of which with survival over 30 days and 203 under 30 days. During the study, we were able to recruit 334 patients (82.2% of the original sample size), 234 of which with survival over 30 days and 100 under 30 days.

Results

Three hundred and thirty-four consecutive advanced cancer patients were included in the analysis; their characteristics are listed in Table 1. Median age was 72 years (range 26–99), and median overall survival was 14 days (range 0–544), with 17 and 9 days in the Palliative Care Unit of Udine and in the Hospice of Treviso, respectively. Survival estimates, using Kaplan-Meier method, were 30% at 30 days and 16% at 60 days.

Evaluation of the accuracy of the scores in predicting 30-day survival

PaP Score resulted as the most accurate instrument for predicting a 30-day survival in both institutions (total AUC 0.82, 95%CI 0.77–0.86); the AUC were substantially the same in the Hospice and in the "Area Cure Palliative". Concerning the OPS, total accuracy was 0.70 (95%CI 0.64–0.75), with similar results between Hospice and the "Area Cure Palliative."

The overall accuracy of PPI was 0.72 (95%CI 0.67–0.77), AUC was 0.68 (95%CI 0.61–0.74) in the Hospice, and 0.75 (95%CI 0.66–0.82) in the Area Cure Palliative. After applying Bonferroni correction for pair comparison between scores (Wilcoxon's test), a statistically significant difference emerged between PaP and OPS accuracies ($p < 0.001$), whereas the differences of accuracy between OPS and PPI score and PaP and PPI scores were not significant. The results are summarized in Table 2.

Table 1 Characteristics of the patients

Patients characteristics		
	N 334	%
Age (years)		
Median	72	
Range	26–99	
Sex		
Male	176	53
Female	158	47
Overall survival (days)		
Median	14	
Range	0–544	
Site of disease		
Lung	42	12.65
Breast	52	15.66
Colon and rectum	47	14.16
Other	190	57.53
ND	3	
Site of metastasis		
1 site	101	32.79
2 sites	70	22.73
≥ 3 sites	85	27.60
Locally advanced	50	16.88
Oxygen therapy		
Yes	65	19.52
No	267	80.48
Anxiety		
Yes	49	14.67
No	283	85.33
ADL		
0	126	38.89
1	57	17.59
2	58	17.90
3	26	8.02
4	20	6.17
5	19	6.17
6	17	5.25
Albumin (g/L)		
> 25	142	60.17
15–25	71	30.51
< 15	22	9.32
PCR value (mg/L)		
Median	20.1	
Range	0.1–543	
Familial support		
Very good	70	21.26
Good	197	59.28
Poor	65	19.46
Pain (NRS)		
0–3	239	72.29
4–6	58	17.47
7–10	33	10.24

Evaluation of the accuracy of the CPS in predicting 30-day survival

Median value of CPS estimated by nurse and physicians was 3–4 weeks (score 6). A similar accuracy was observed in CPS

Table 2 Accuracy of PaP Score, OPS, PPI, and CPS in predicting 30 days survival

	*Total AUC (95%CI)	Hospice AUC (95%CI)	ACP*** AUC (95%CI)
PaP Score	0.82 (0.77–0.86)	0.82 (0.74–0.87)	0.81 (0.73–0.88)
	$n = 278$	$n = 162$	$n = 116$
OPS	0.70 (0.64–0.75)	0.70 (0.62–0.77)	0.68 (0.58–0.77)
	$n = 278$	$n = 165$	$n = 113$
PPI	0.72 (0.67–0.77)	0.68 (0.61–0.74)	0.75 (0.66–0.82)
	$n = 330$	$n = 213$	$n = 117$
CPS**	Py 1: 0.77 (0.72–0.81)	Py 1: 0.76 (0.70–0.82)	Py 1: 0.83 (0.75–0.89)
	$n = 327$	$n = 211$	$n = 116$
	Py 2: 0.76 (0.71–0.81)	Py 2: 0.75 (0.68–0.82)	Py 2: 0.80 (0.71–0.88)
	$n = 258$	$n = 162$	$n = 96$
	Nurse: 0.78 (0.72–0.82)	Nurse: 0.75 (0.67–0.81)	Nurse: 0.83 (0.74–0.91)
	$n = 257$	$n = 165$	$n = 92$

*$p = 0.0001$ for comparison of AUC of the three scores

**For comparison of the three CPS (physician 1, nurse, and physician 2), p value is 0.719

***ACP, "Area Cure Palliative"

estimation by the three operators: AUC 0.78 (95%CI 0.72–0.82) for the nurse; 0.77 (95%CI 0.72–0.81) for physician 1; and 0.76 (95%CI 0.71–0.81) for physician 2.

In detail, accuracy expressed by physicians and nurse in the hospice and in the palliative care unit is represented in Table 2 and Fig. 1.

Evaluation of agreement between the estimated and the real/actual survival and between the operators

The agreement between the CPS and the real survival (expressed by k value) was 0.42 (95%CI 0.33–0.53) for physician 1, 0.40 (95%CI 0.31–0.47) for physician 2, and 0.44 (95%CI 0.38–0.52) for the nurse. Taking in consideration the level of experience of physician 1, a slightly better agreement emerged for operator with more than 10 years of experience, even in comparison with nurses' estimation (k value: 0.45, 95%CI 0.25–0.67).

The agreement between nurse and physicians was good, based on k values of 0.71 between nurse and physician 1 and 0.78 between nurse and physician 2; the agreement between the two physicians was also good (k 0.81).

Counterintuitively, our analysis revealed that all operators tended to underestimate the patients' life expectancy ($p = 0.01$ for physician 1, $p = 0.061$ for physician 2, $p = 0.044$ for nurse).

Potential prognostic factors for 30-day survival and for overall survival

Clinical data and serological results studied as potential prognostic factors were the number of metastatic sites, the presence of pain, anxiety and/or delirium, the need for oxygen supplementation, ADL score, albumin plasmatic values, and CRP.

In univariate analysis, the ADL score (considered as continuous variable) and the presence of anxiety were associated with lower 30-day survival rate, with OR 0.70 (95%CI 0.62–0.80; $p < 0.001$) and OR 4.45 (95%CI 1.71–11.58; $p = 0.002$), respectively; therefore, poor survival was associated with reduced ADL scores and with the presence of psychological suffering. In addition, the number of metastatic sites was associated with survival: the presence of more than three sites of metastases correlated with poor prognosis (OR 4.41, 95%CI 2.09–9.32, $p < 0.001$). In multivariable analysis, only the ADL score and a number of metastatic sites greater than 3 retained their statistical significance (OR 0.71, 95%CI 0.60–0.85, $p < 0.001$ and OR 4.39, 95%CI 1.81–10.67, $p = 0.001$, respectively).

Similar results were observed for variables that predict overall survival. In univariate analysis, having a lower ADL score and more than three metastatic sites correlated with shorter survival (HR 0.86, 95%CI 0.81–0.92, $p < 0.001$ and HR 1.70, $p = 0.001$, 95%CI 1.26–2.30, respectively), these results are confirmed in multivariable analysis (HR 0.84, 95%CI 0.78–0.91, $p < 0.001$ and HR 1.49, 95%CI 1.01–2.21, $p = 0.042$ respectively). The results are summarized in Table 3.

Discussion

In this study, PaP Score was found to be the most accurate tool in predicting survival at 30 days. According to literature data, this result confirms the validity of this instrument and its superiority when compared with other newer scores such as the OPS and the PPI.

While PPI is based only on clinical parameters and OPS is mainly funded on laboratory variables, PaP Score includes

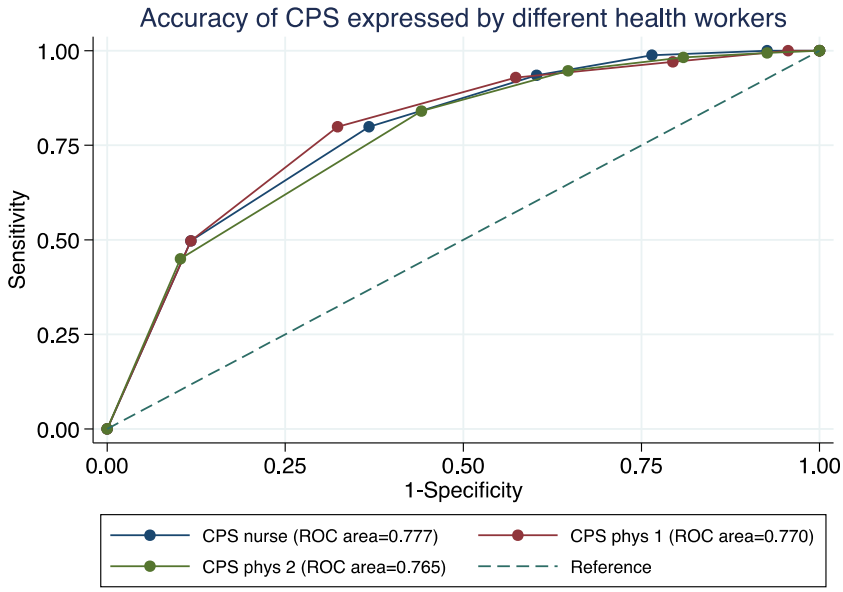

Fig. 1 Accuracy of CPS expressed by different health workers

both clinical and hematological parameters, proving to be a more exhaustive instrument of prediction.

In our study, PaP Score was not calculated for 17% of patients and the main reason was the lack of laboratory data especially for hospice-based series; PPI in these cases showed also a good accuracy. Finally, our prospective study demonstrated that PaP Score predicts the likelihood of survival at 30-days but we need other new tools to predict survival at further time points.

Regarding CPS, operators estimated more frequently a survival of 3–4 weeks and the level of accuracy were similar between health professionals. We found a moderate degree of accuracy in predicting a 30-day survival, which was highly concordant among the three operators.

Nurse's estimation had the highest agreement with real survival and the highest accuracy in predicting a 30-day survival; although the differences were not statistically significant, they can reflect the key role of these health professionals in palliative care setting. In fact, they spend more time with patients than physicians do; they may have a more comprehensive understanding of the overall patients' needs and more easily communicate with their families. Even if this close relationship may help specialized nurses, better understanding the disease's evolution is however uncertain.

Counterintuitively, the correlation between estimated and actual survival demonstrated a tendency to underestimate the prognosis, revealing a pessimistic operators' attitude. In previously published studies, health professionals who have taken care of patients from the very beginning of their illness and built with them a deep relationship tended to overestimate their expected survival [31]. Instead, the operators involved in this study were not the same that cared the patients from the diagnosis of cancer, so their estimation of the prognosis could markedly differ.

Another important factor is the experience of operators; this study confirms that lack of clinical experience is associated with less accurate prediction.

The accuracy of CPS in predicting 30-days survival is high in our work. We recognize that the accuracy of PaP Score may be influenced by this data.

Table 3 Potential prognostic factors for 30-day survival and overall survival in univariate analysis

	Potential prognostic factor		30-day survival		Overall survival	
			OR (95%CI)	*p*	HR (95%CI)	*p*
Univariate analysis	ADL	(*)	0.70 (0.62–0.80)	< 0.001	0.86 (0.81–0.92)	< 0.001
	Anxiety	Yes	1.00	–	1.00	–
		No	4.45 (1.71–11.58)	0.002	1.56 (1.14–2.13)	0.006
	Number of metastatic sites > 3	1	1.00	–	1.00	–
		2	1.76 (0.91–3.41)	0.093	1.25 (0.91–1.71)	0.161
		≥ 3	4.41 (2.09–9.32)	< 0.001	1.70 (1.26–2.30)	0.001
		Locally advanced	0.98 (0.49–1.97)	0.963	0.92 (0.65–1.31)	0.638

(*), Continuous variable

The degree of patient's autonomy and a number of metastatic sites more than three were independent prognostic factors for 30 days and overall survival in multivariable analysis. These easy-to-collect parameters are important data to register at the time of admission and reinforce the need for rehabilitation of cancer patients.

According to previous reports, the presence of anxiety, pain, the need for oxygen, and the degree of family support did not show a prognostic value in multivariable analysis [4, 16, 32]. Although the influence of coping and emotional distress on survival in cancer patients is controversial, previous trials showed that depression increases the risk of quality of life deterioration and disease-related mortality [4, 33]. Systemic inflammation has been shown to predict survival in patients with a variety of common solid tumors [34], regardless of disease stage and pathological characteristics; in our study, however, the levels of CRP or albumin were not prognostic. A possible explanation is the lack of laboratory tests for some patients (around 15%); moreover, the median survival in our study was 14 days, whereas median survival in other trials was superior. We can hypothesize that serological results are less important prognostic factors in terminally ill disease patients, for whom clinical conditions (represented by PS, ADL score, or the presence of anorexia-cachexia syndrome) become more important.

Our prospective study has also some limitations. It was not possible to collect all the data to estimate the PaP Score and the OPS for the whole population; moreover, data were collected in two different structures: different training and attitude of operators may have influenced the prognostic estimation. In addition, we acknowledge that although we have undertaken a multivariable analysis of prognostic factors, our model was not validated with an independent cohort of patients.

Providing an accurate prognosis for advanced cancer patients is a critical issue for all physicians; prognostication, however, may be particularly challenging because it is a process instead of an event and it may change over time depending on treatment response, development of acute oncological complications, or competing comorbidities. A variety of prediction tools have been developed to help clinicians refining the life expectancy estimation [31].

In accord with literature data, clinical prediction of survival maintains a moderate degree of accuracy, but a multidimensional score (in this case, the PaP Score) is more useful in terms of prognostic estimation [35, 36].

In a prospective observational cohort study, Gwilliam et al. evaluated 1018 advanced cancer patients referred to palliative care services with the aim to develop a novel prognostic indicator. Two different models were created for patients with or without blood results showing that a combination of clinical and laboratory variables might reliably predict survival at 2 weeks and 2 months [37].

The change in a prognostic score over the time may also be useful for predicting survival, with the evidence that patients who deteriorate often have a worse prognostic score over time; Kao et al., in a study of 2392 patients, found that the median PPI increased from 6 on day 1 to 7 on day 8 ($p < 0.001$) [38]. The median survival rate was 53 days with an improvement in PPI score, 36 days with a stable PPI score, and 22 days with PPI deterioration over 1-week period; a change in PPI over only 1 week had prognostic value.

Conclusions

In our study, Pap Score emerged as a complete tool in the prognostic evaluation of cancer patients with advanced disease and it showed the best value of accuracy when compared with other prognostic tools (PPI and OPS), but may not be the most appropriate for out- or hospice patients. When the lack of lab test does not allow calculating the Pap Score, the PPI may be considered; however, novel prognostic and nutritional factors may to be included in a multidimensional model.

The accuracy of CPS in predicting survival can be improved by closer cooperation between all the health professionals who care for the patient; interventions to train inexperienced operators to make better predictions are crucial. Finally, the patient's autonomy was an important prognostic factor. This result emphasizes the importance of stimulating the remaining autonomy as possible and the importance of rehabilitation in palliative care setting.

More studies are needed to examine how prognostic tools can be integrated to guide palliative care referral and chemotherapy discontinuation [31], as well as to improve the prognostication ability and the communication skills.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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