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The Development of the Prognostat Tool for Survival Prediction in Palliative Care Patients

Downing GM[*1], Lesperance M[2], De Kock I[3], Mirhossein M[4], Black F[5] and Lau F[6]

[1]Clinical Associate Professor, University of British Columbia, Faculty of Medicine, Dep't of Family Medicine, Division of Palliative Care, Vancouver, Canada; Adjunct Assistant Professor, University of Victoria, School of Health Information Science; Palliative Medicine, BC Cancer Agency Pain & Symptom/Palliative Care Clinic, Victoria, BC
[2]Professor, University of Victoria, Department of Mathematics and Statistics, Victoria, BC, Canada
[3]Clinical Professor, University of Alberta, Division of Palliative Care Medicine, Dep't of Oncology, Edmonton, Alberta, Canada
[4]Clinical Associate Professor, University of Alberta, Division of Palliative Care Medicine, Dep't of Oncology, Edmonton, Alberta, Canada
[5]Clinical Associate Professor, Assistant Dean, University of Victoria, Island Medical Program; Palliative Care Physician, Victoria Hospice Society, Victoria, BC, Canada
[6]Professor, University of Victoria, School of Health Information Science, Victoria, BC, Canada

[*]**Corresponding author:** Downing MG, BC Cancer Agency, Lee Ave, Victoria, BC, Canada, Tel: 250-516-3544, E-mail: drgmdowning@gmail.com

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Abstract

Background: Since a common question arises toward end of life about prognosis and that clinicians vary widely in the accuracy of their survival predictions, it is important that advancements be developed, one of which is to design or improve prognostic tools.

Purpose: To test the reliability of the new Prognostat tool for survival prediction in palliative care patients

Design: Prospective multi-site mixed methods study with data collection, survey and focus groups.

Setting: Prognostat form completed during first assessment by a palliative physician or nurse on admission to a palliative care unit or first ward or home consult.

Results: Four sites were involved with Prognostats completed on 422 patients by 24 palliative clinicians. Of these, the median age was 70 years, 83.2% cancer/16.8% non-cancer, and 29 were censored. Only 5 of 15 factors tested were significant in the multivariable model including clinician prediction of survival, Palliative Performance Scale (PPSv2), primary illness, gender and delirium. Non-significant factors were illness trajectory, age, Charlson Index, tiredness, weight loss, loss of appetite, peripheral edema and skin breakdown. The final model with 5 variables had a Harrell's C of 0.78 demonstrating good predictive discrimination of the model. Focus groups liked the calculator table and nomogram graph in preference to KM-graphs, and the Prognostat was felt to be somewhat valuable, easy and non-invasive tool. Limitations include defining the term 'palliative,' chosen prognostic time intervals and small validation group.

Conclusion: The preliminary Prognostat is shown in this study of patients already registered or referred to palliative care to be a significant predictor of survival and may assist in clinical prognostication. Surprisingly, several factors such as Charlson comorbidities were not significant factors. For practical use, clinicians preferred the table and graph nomograms for quick estimation of survival. Further study is warranted to validate the tool.

Keywords: Palliative; Hospice; Prognostication; Survival prediction; Palliative Performance Scale

Introduction

Prognostication is a challenging yet important issue for those with progressive advanced and life-limiting illnesses. At some point, the patient or family may ask "Doc, how long do I have?" [1] and our response affects decisions about continuing or stopping treatments, timing of travel of family to visit, location of care and service needs to name a few. Several tools are currently in use which employ various parameters to estimate survival including the Palliative Prognostic Score (PaP) [2-8], Palliative Performance

Index (PPI) and Prognosis in Palliative Care Study (PiPS)[9-12].

The Palliative Performance Scale (PPSv2) has also been shown to be a significant predictor of survival for palliative care patients [4,9,11,13-18]. Yet, the clinician's prediction of survival (CPS) is also important albeit with varying accuracy [19-21]. Many clinicians are able to categorize patients in terms of how sick they are or how long they have to live [22] with some discriminatory abilities but as Justice [22] notes they are not well calibrated [23,24]. To improve precision several laboratory marker indices have been incorporated into some prognostic tools such as low albumin [25], elevated lactate dehydrogenase [25], elevated white cell count combined with lymphocytopenia [26-28], levels of B12, CRP [24,29] and others.

The Palliative Performance Scale (PPS) is known to be a significant predictor of survival for palliative care patients [4,9,11,13-17,30,31]. Although PPS contains both functional assessment and other components of level of consciousness and intake, there are likely also other important factors. The Prognostat was developed to incorporate and test several additional factors reported in the literature.

The Charlson Co-morbidity Index (CCI) is a commonly used tool in chronic disease that includes 19 co-morbidities which have been shown to have prognostic significance value in multiple studies [32-40]. To our knowledge CCI has not yet been incorporated into specific palliative prognostic tools and thus warrants testing. Also, the general trajectory of an illness is an important factor that clinicians use in daily assessment and has shown to have some predictive ability particularly if a sudden functional decline occurs [30]. The Australian 'illness phases' utilizes five aspects of an illness including pre-death categories of stable, unstable, deteriorating, terminal and also bereavement [41,42]. Since palliative care patients face gradual, progressive or sudden decline with the emergence of symptoms leading to death, the inclusion of a trajectory variable into prognostic tools is important to study.

In general, the intent of such tools is not to predict the actual date of death but to involve a probabilistic approach where the 'likelihood' of survival is improved using grouped patient data and prediction graphs and tables. However, Stiel notes that scoring systems on prognosis of survival time seem to be least useful for those patients with neither a good nor a poor prognosis where in those situations both physicians' estimates as well as the existing prognostic instruments lack precision [43]. In other words, clinicians seem to predict quite well if the patient is very close to death or if they are very stable and doing well; it is the 'in-between' that remains challenging. Much attention has recently focused on the 'surprise question' stated as "Would you be surprised if your patient died within the next 6 or 12 months?". This appeared somewhat useful in cancer [44], renal [45,46] and ICU [47] patients.

The Prognostat is a new tool combining several factors and designed to be easy, quick and non-invasive. The primary research question is whether the Prognostat is a significant predictor of survival and secondly, do new variables such as CCI and illness trajectory add significant value to survival prediction in palliative patients?

Methodology

Prognostat Test Model

The Prognostat exploratory model combined PPS with clinician prediction of survival(CPS) [4,20,48-50], nineteen co-morbidity factors incorporated into the weighted Charlson Co-morbidity Index (CCI) [35,37,40,51,52], seven symptoms [53-55] and four Australian illness 'phases' [42,56,57]. These variables are defined in Table 1 and were selected by an interdisciplinary palliative expert group of 12 physicians and nurses. Further Delphi-type feedback was gained from two workshops [58] where it was also recommended that prognostic tools be quick, easy to use and preferably non-invasive, so laboratory markers were excluded as being minimally invasive. The CPS was categorized into clinically relevant time blocks. The outputs to be explored in the Prognostat included a life expectancy table calculator, nomogram and Kaplan-Meier graphs similar to our prior work [59].

Palliative Performance Scale (PPSv2)	PPS is a functional status and survival prediction tool. Use instructions for PPSv2 for eleven categories from PPS 100% to PPS0% in 10-percent increments [13].
Australia Illness Trajectory or Phase	**Stable:** All patients not classified as unstable, deteriorating, or terminal. Symptoms are adequately controlled by established management. Further interventions to maintain symptom control and quality of life have been planned. Functional status remains same or may improve.
	Unstable: the development of a new unexpected problem or a rapid increase in the severity of existing problems, either of which require an urgent change in management or treatment
	Deteriorating: a gradual worsening of existing symptoms, functional status or the development of new but expected problems. These require the application of specific plans of care and regular review but not urgent or emergency treatment
	Terminal: death is likely in a matter of days and no acute intervention is planned or required (PPS 10%-20%)
Clinician Prediction of Survival	Taking into account the patient's history, the present stage of illness, potential for treatment response, physical assessment and overall clinical experience, the clinician makes an overall judgment of the likelihood of dying within one of the 6 time periods listed. Depending on individual circumstances, the time period may be up to 24 hours if investigations were ordered and deemed important in judging options for treatment and need to revise clinical prediction of survival. The following categories are to be used: <3days, 4-7 days, 1-4 weeks, 1-3 months, 4-6 months and >6 months

Charlson Co-Morbidity Factors [examples only of 19 factors]	• **Renal – moderate** Stage 3 (GFR 30-60ml) or Stage 4 (GFR 15-30) to **severe** Stage 5 (GFR < 15 ml/min – renal failure - dialysis) • **Liver** – moderate to severe implies degrees of cirrhosis, encephalopathy, portal hypertension, etc along with abnormal albumin, INR, bilirubin, ammonia, etc
Delirium	An acute brain syndrome or confusional state as defined by the ICD-10 diagnostic guidelines. The recent onset of change in mental status may be due to several factors eg. sepsis, electrolyte imbalance, renal failure or drug toxicity. It may be mild to severe, hypo- or hyper-active in type.
Dyspnea on exertion	This is difficulty breathing on exertion (moderate or severe on a verbal scale or ≥4/10 on a ESAS) expressed by the patient or observed when the patient attempts to increase physical activity. This would include either activity such as walking, standing or a bed-bound patient who tries to change position or even tries to talk. The patient may or may not be receiving oxygen and may or may not be dyspneic at rest
Weight loss	Approximately 5% or more loss of weight compared to the previous three months or so.
Peripheral Edema	Primarily meant as dependent edema, especially in the feet, legs or pelvis. Various causes include hypoalbuminemia, congestive heart failure, cirrhosis or renal failure. It does **not** include unilateral edema due to lymphatic blockage or upper extremity edema in the absence of lower leg edema.
Skin Pressure Ulcer	This is skin breakdown due to pressure &/or sheering. The location may be sacral decubitus or heel, elbow, scapula or other. It includes any of the 4 stages of skin ulcers but does **not** include fistula or peri-ostomy skin breakdown
Persistent Tiredness	Persistent tiredness (rated at moderate to severe verbal or ≥4/10 on a numerical or ESAS scale), and in general present for past weeks to few months
Loss of Appetite	This means a significant decrease in appetite (moderate to severe verbal or ≥4/10 on a numerical or ESAS scale) over recent weeks. It may or may not include cachexia and may or may not result in actual reduced intake or weight loss

Table 1: Definitions for Prognostat Variables in the Test Model

Data Analysis

The palliative patient was defined as either being the first admission to a palliative care unit or hospice, or received a palliative consultation at home or hospital. A Prognostat collection form (Supplementary XX) was used by palliative physicians and nurses to obtain data from patients including their survival predictions at the time of first admission or consult. Data was entered into Microsoft (MS) Access, anonymized and extracted for analysis.

Descriptive statistics, Kaplan-Meier survival curves and log-rank statistics were computed. The Cox proportional hazards model was fitted to the survival outcomes incorporating the Prognostat component variables together with the demographic variables, age, gender, location and disease. The statistical significance of Prognostat components for predicting survival were assessed using Wald tests for the corresponding (log)-hazard ratios. A backwards elimination process was used to formulate a final survival prediction model. Survival nomograms were generated using Harrell's Design library for R [60] which incorporates Cox model analyses to compute weights that are applied to the Prognostat components to determine an overall Prognostat Score. Computations were performed using R2.12.1 and SPSS V17.

Sample size was calculated using Harrell's [60] recommendations of ten events (deaths here) per model parameter. We thus required over 300 deaths to accurately estimate the initial variables with parameters including PPS 9, CPS 5, illness trajectory 4, seven symptoms, CCI 4, age, gender, primary illness and location. Once the total number of cases was met (8 months), recruitment was stopped and four additional months were allowed to follow survival on the remaining cases.

The study participants were also sent a short satisfaction survey which was used along with three focus groups to assess utility of the Prognostat. This qualitative data was thematically analyzed and used along with three separate focus group sessions. Invitations for these focus groups included all study participants in the three city locations. The questions and results can be seen in the Supplementary data regarding clinical relevance and utility.

Ethics

Ethics approval was received by the Health Research Boards of the University's of Victoria (#J2009-38) and Alberta (#Pro00007680), with some funding from the Canadian Institutes for Health Research (CIHR)) Partnership in Health System Improvement (PHSI) grant on Timely Access to End-of-Life Care (PHSI#33928-54150) and the Victoria Foundation's Myre & Winnifred Sim fund.

Results

Four locations participated: two with Palliative Care Units (PCU) only (Nanaimo, Saanich) and two with combined PCU, home and ward consult services (Victoria, Edmonton) but one PCU withdrew after a few cases. There were 25 physician and 20 nurse participants. There were 518 prognostats completed in 422 patients but in those additional situations, assessments were performed by both physician and nurse independently and a few patients had repeat assessments at a later time point or different location of

care. The analysis was conducted on only the 422 patient first assessments. Demographic characteristics are shown in Table 2. The average age was 70 years, with the primary disease of cancer 83.6%, non-cancer 16.4%. The time from first Prognostat completion until death (or censoring) averaged 38 days (median 10 days). There were 29 Prognostats censored at study closure.

Variable	Value	Prognostat Test Set		Validation Set	
		Count	%	Count	%
Gender	Male	223	53.1%	29	46.0%
	Female	197	46.9%	34	54.0%
	Not recorded	2	0.3%	0	-
Age	< 45 yrs	14	3.3%	1	1.6%
	45-64 yrs	142	33.6%	7	11.1%
	65-74 yrs	95	22.5%	4	6.3%
	75-84 yrs	96	22.7%	9	14.3%
	85+ yrs	67	15.9%	7	11.1%
	Not recorded	8	1.9%	35	55.6%
	Mean age	69.5	-	74.0	-
	Median age	71.0	-	75.5	-
Primary Illness	Non-cancer	71	16.8%	11	17.5%
	Ca Lung	73	17.3%	21	33.3%
	Ca Colorectal	38	9.0%		
	Ca Breast	30	7.1%	7	11.1%
	Ca Prostate	29	6.9%	2	3.2%
	Ca Other	174	41.2%	22	34.9%
	Not recorded	7	1.7%	0	-
Location at 1st Assessment	Alive	25	5.9%	1	1.6%
	Died	397	94.1%	62	98.4%
	Pall Care Unit	162	38.4%	26	41.3%
	Home	155	36.7%	1	1.6%
	Ward/ER	82	19.4%	36	57.1%
	Residential Hospice	23	5.5%	0	-
Location of Death	Pall Care Unit	226	53.6%	-	-
	Home	86	20.4%	-	-
	Ward/ER	43	10.2%	-	-
	Residential Hospice	33	7.8%	-	-
	Missing data	34	8.1%	-	-
Site	Victoria	241	57.1%	-	-
	Edmonton & Nanaimo	181	42.9%	-	-

Table 2: Demographics of test and validation samples

Table 3 shows the frequencies and percentages for the clinical variables used in the study. In the interest of parsimony, we aggregated levels of PPS into clinically relevant groups: PPS 10-20%, PPS 30-40%, PPS 50% and PPS 60% or higher. CPS categories were collapsed at each end from focus group discussion. A backwards elimination process was used to formulate a survival prediction model. Factors found not to be significant in the multivariable Cox model include: illness trajectory, location of care, dyspnea on exertion, age, Charlson Index, persistent tiredness, weight loss, skin pressure sore, loss of appetite and peripheral edema. Statistically strong factors include CPS, PPS, gender, primary illness and, delirium. P-values for these variables included in the survival prediction model are listed in Table 4. Harrell's C-stat is 0.78 which shows good predictive discrimination of the model.

Variable	Value	Prognostat		Validation Set	
		Count	%	Count	%
Clinician Prediction of Survival (CPS)	≤ 7 days	121	28.7%	11	17.5%
	1-4 weeks	111	26.3%	21	33.3%
	1-3 months	136	32.2%	24	38.1%
	≥ 4 months	52	12.3%	7	11.1%
	Not recorded	2	0.5%	0	-

Variable	Value	Prognostat		Validation Set	
		Count	%	Count	%
Palliative Performance Scale (PPS)	PPS 70%	16	3.8%	4	6.3%
	PPS 60%	38	9.0%		
	PPS 50%	65	15.4%	13	20.6%
	PPS 40%	113	26.8%	37	58.7%
	PPS 30%	89	21.1%		
	PPS 20%	40	9.5%	9	14.3%
	PPS 10%	61	14.5%		
Illness Trajectory	Stable	51	12.1%	1	1.6%
	Unstable	98	23.2%	8	12.7%
	Deteriorating	182	43.1%	44	69.8%
	Terminal	89	21.1%	10	15.9%
	Not recorded	2	0.5%	0	-
Primary Illness	[see table 2]				
Location of Care	[see table 2]				
Gender	[see table 2]				
Age	[see table 2]				
Delirium	No	307	72.8%	44	69.8%
	Yes	115	27.3%	19	30.2%
Dyspnea on exertion	No	206	48.8%	40	63.5%
	Yes	216	51.2%	23	36.5%
Charlson Co-Morbidities	0	51	12.1%	-	-
	1-4	136	32.2%	-	-
	5-9	208	49.3%	-	-
	10-15	27	6.4%	-	-
Weight loss	No	160	37.9%	-	-
	Yes	262	62.1%	-	-
Loss of appetite	No	110	26.1%	-	-
	Yes	312	73.9%	-	-
Peripheral Edema	No	266	63.0%	-	-
	Yes	156	37.0%	-	-
Skin Pressure Sore	No	366	86.7%	-	-
	Yes	56	13.3%	-	-
Persistent Tiredness	No	103	24.4%	-	-
	Yes	319	75.6%	-	-

Table 3: Model with 15 Variables Included in the Exploratory Prognostat Model

Factor	P value
Clinician Prediction of Survival (CPS)	<.0001
Palliative Performance Scale (PPS)	0.0008
Primary Illness	0.0265
Gender	0.011
Delirium	0.0299

Table 4: Wald Statistics for Model Variables in Final Prognostat

The final Prognostat nomogram in table calculator format is given in Table 5. Each variable has a weighted value and these are summed to create a total points score. By then locating that score on the percentile table, the likelihood of dying is shown by 10th, 25th, median, 75th and 90th percentile predictions.

Prognostat predictions were considered accurate if the observed survival time fell between the estimated 25th and 75th percentiles. The CPS was considered accurate if actual survival time fell within the CPS interval in the Prognostat that the clinician indicated. From this, 42% of CPS values were accurate compared to 69% accuracy using the Prognostat. The final Prognostat model was

validated using external prospective data. There were 63 patients in the validation set for whom descriptive statistics are provided in Tables 2 and 3. Since the validation model only collected 'points', we could not distinguish colorectal from lung cancer in Table 2. For the validation set, 69% of CPS values were accurate compared to 84% accuracy using the Prognostat.

Category Point Scores for Prognostat			Total Points Ranges	Prognostat Survival Table # Days Likelihood until Death by Percentiles				
Category	**Factor**	**Points**		**10th**	**25th**	**Median**	**75th**	**90th**
Clinician Prediction of Survival (CPS)	≥4mos	0 points	<10	**>10**	>45	>150	-	-
	1-3mos	22 points	10's	**10**	45	150	-	-
	1-4wks	42 points	20's	**8**	35	120	-	-
	≤7days	100 points	30's	**7**	30	90	>210	-
Palliative Performance Scale (PPS)	PPS ≥60%	0 points	40's	**6**	20	60	210	-
	PPS 50%	20 points	50's	**5**	15	60	120	-
	PPS 30-40%	35 points	60's	**4**	10	45	120	>210
	PPS 10-20%	53 points	70's	**3**	9	30	90	210
Primary Illness	Ca Breast	0 points	80's	**3**	7	30	60	120
	Ca Prostate	5 point	90's	**3**	6	20	45	90
	Non-Cancer	9 points	100's	**2**	5	15	30	90
	Ca Other	22 points	110's	**2**	4	10	30	60
	Ca Colorectal	32 points	120's	**2**	3	8	20	45
	Ca Lung	32 points	130's	**2**	3	7	15	30
Gender	Female	0 points	140's	**2**	3	5	15	30
	Male	16 points	150's	**1**	2	4	10	20
Delirium	No	0 points	160's	**1**	2	4	8	15
	Yes	14 points	170's	**1**	2	3	6	10
Using the categories and definitions of terms: o Obtain a **Category Point Score** for each and then sum these to obtain a Total Points Score o Locate the **Total Points Score** (to the closet 10-point value) and view the Survival Percentiles			180's	**1**	2	3	5	9
			190's	**1**	1	3	4	7
			200's	**0**		2	3	6
			210's	-		-	-	5
			Prognostat© 2013. M. Downing, Victoria Hospice Society, 1952 Bay St, Victoria, BC, Canada, V8R 1J8					

Table 5: Prognostat Calculator Table

A survey and three focus groups were held totalling 15 palliative physicians and 11 palliative nurses to discuss preliminary results, and from which several themes emerged. The tool was felt to be "somewhat or very" easy (79%), quick (83%), "somewhat or very" useful (78%) and practical (62%). Overall, the Prognostat was felt to be a valuable tool which enhances a clinician's prediction of survival. The nomogram and the calculator table were the preferred methods to use the tool, and KM-graphs least preferred. Specific information on the survey and nomgram graph is found in Supplementary data.

Discussion

The Prognostat improved standalone reports of survival prediction for both clinician prediction (CPS) and PPS scores [31,50,53]. Primary illness, gender and delirium added further significance while surprisingly; the Charlson Index [33] was not significant in our model. Although other studies in cancer and non-cancer have shown the CCI to be a significant factor, an external palliative physician not involved in this study (personal communication) suggested that in far advanced illness these factors are 'washed out' by more significant changes in functional status and clinician prediction. Further study is warranted to clarify this.

The cancer categories were selected using the four with the highest mortality in Canada. The 'other' cancers accounted for more cases but varied highly so they were grouped for statistical purposes. Although the 71 non-cancer cases were only 16.8% of the total, that is similar to the number of lung cancer patients. Further, on the nomogram, 'non-cancer' is significant and lies between cancer of the prostrate and other-cancers. This suggests that non-cancer illnesses can be fitted into prognostic tools and that such patients do not always live longer than cancer patients. A larger sample size is needed to test significance for non-cancer illnesses as well as delineate among other primary cancers (eg. Harris et al) [61].

Neither the Charlson CCI nor Australian trajectory phases were significant in the 422 cases. Interestingly however, we initially analysed the 518 cases which included some 'repeat' cases and both parameters were significant. The repeat cases were removed from the final analysis to preserve statistical accuracy of 'first' assessment predictions. Further studies using prospective serial assessments are imperative. An earlier model of the Prognostat was less predictive but did not include CPS [62].

An ongoing issue in this field is to adequately define what constitutes the term 'palliative patient.' We based this on direct involvement with "palliative experts" either by referral for consultation or admission to a palliative care unit or hospice. Such referrals usually occur in advanced illness which fits the shorter lengths of stay and survival seen in many palliative prognostic tools [6-11,63-65]. However more recent evolution in this field frequently uses a 'palliative approach' which implies a much broader interpretation of the term palliative, makes identification and prognostication more challenging. The 'surprise question' is often utilized about the 'risk' of dying but appears limited on its own as a survival prediction tool [66-70].

Clinician prediction of survival (CPS) remains a valuable aspect in prognostication being the most significant of all variables in this study. Accuracy was substantively improved by 15%-27% in the two datasets using the Prognostat with an overall accuracy of 69-84%. Additionally it provides quantiles of risk which may be clinically informative. Also, the percentile scores were highly appreciated in showing a clinically practical range of survival predictions including both 10% and 90% blocks.

Limitations of study

Since the final Prognostat model was reduced from 15 variables to 5, there is need for a larger prospective validation study. Although definitions were provided, the focus groups noted some ambiguity with several symptoms such as tiredness, weight loss and dyspnea.

The prognostic time intervals were also at question. Some focus group participants suggested using simple groupings of days, weeks or months but there was no agreement. The issue is similar to variations seen in other tools such as PaP [6,7] and PiPS [12]. As with most palliative care studies in advanced stage illness, patients had a shorter overall prognosis; we had insufficient cases in those living six months or more category and thus were collapsed into >4 months category. A larger study is needed to gain significant longer-term survivors.

Although our overall Kaplan-Meier mean and median survival times are short at 44 and 12 days respectively, these are similar to several other palliative prognostic tools. For example, the PaP tool is based on 30-day survival [7] and PiPS categories' median survivals are 5, 33 and 92 days [12]. Therefore the findings may not apply to early stage illness where patients are not admitted to palliative programs or not referred for palliative consultation.

Finally, the patients were already deemed palliative, generally with far advanced illness and either seen in consultation by palliative physicians or admitted to a palliative care unit. Therefore, the findings may or may not apply to patients who are only "at risk of dying," "not palliative" or not seen by palliative expert clinicians.

Conclusion

The Prognostat appears to be a significant predictor of survival for patients already deemed palliative but requires further validation. The study adds support for probabilistic tools using a calculator nomogram with a range of survival percentiles within the individual patient parameters. At least for now the Charlson comorbidities, Australian phases, tiredness, appetite and weight loss are not shown to be the predictors of survival but need to be tested in a larger prospective validation study.

The nomogram table calculator is preferred by most clinicians over KM-graphs. The Prognostat is a simple, non-invasive tool that can assist clinicians in prognostication for palliative patients. Future study should include serial calculations for trajectory analysis and repeat of the Australian phases may demonstrate value in larger cohorts and comparison among professionals. Branco study.

Declaration

The authors declare there are no competing financial interests.

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Supplementary data

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