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REVIEW ARTICLE **CME**

Accuracy of Clinicians' Prediction of Survival and Prognostic Factors Indicative of Survival: a Systematic Review

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ABSTRACT

Objectives: *To review the literature and examine the accuracy of clinicians' prediction of survival as well as prognostic factors determined to be predictive of shorter survival in terminal cancer patients.*

Methods: *A literature search was conducted on MEDLINE (1 January 2000 to 29 July 2012), Embase (1 January 2000 to 22 July 2012), and Cochrane Database of Systematic Reviews (1 January 2005 to July 2012). Reference sections of relevant reviews were also examined for relevant articles. All studies examining the accuracy of prediction of survival and prognostic factors indicative of survival in patients with terminal cancer were selected. Descriptive statistics summarised the extracted data.*

Results: *A total of 85 studies published from 1972 to July 2012 with a study cohort of 30 to 6066 patients were identified. Clinicians' prediction of survival correlated with patient's actual survival, but the predictions tended to be too optimistic. The ability of varying health care professionals to estimate survival was contradictory among different studies. Some studies noticed those with more experience with terminal cancer patients were better able to predict an accurate estimation, whereas others concluded that there was no difference. The estimations were also more accurate during short-term time ranges such as the 'horizon effect'. Only a few assessment tools to assist in predicting the remaining duration of survival in patients were validated. A variety of prognostic factors between studies were identified, but the factors were not validated nor any instruments created.*

Conclusion: *Demographic information and clinical symptoms can assist in determining the remaining duration of survival of terminal cancer patients. Assessment tools should be convenient and not a burden for the patient as the goal of palliative care is to maintain or improve the quality of life as much as possible. Even with the application of instruments to formulate a prediction, error cannot be completely eliminated. Physicians should warn the patient and their family of the uncertainty of the predictions.*

Key Words: *Neoplasms; Prognosis; Survival; Terminal care; Terminally ill*

中文摘要

臨床醫生預測生存期的準確度及預後因素：系統性綜述

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目的：回顧文獻並調查臨床醫生對晚期癌症患者生存期的預測準確度及較短生存期的預後因素。

方法：文獻檢索MEDLINE（2000年1月1日至2012年7月29日）、Embase（2000年1月1日至2012年7月

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22日）和Cochrane系統評價數據庫（2005年1月1日至2012年7月）的資料，並一併回顧所選取文獻中的參考文獻資料。選取所有調查晚期癌症患者生存期的預測準確度及預後因素的研究。描述性統計總結提取的數據。

結果：共發現於1972年到2012年7月期間發表，病人數目從30至6066名不等的85項隊列研究。將臨床醫生預測的生存期與病人實際生存期做相關性分析，發現預測往往過於樂觀。不同醫療保健專家對不同研究中生存期的估計存在矛盾。一些研究發現在晚期癌症患者方面經驗更豐富的臨床醫生能更準確地預測生存期，而另外一些研究得出的結論是兩者並無差異。此外，在短時間範圍內的估計也會更準確。用作幫助預測患者生存的剩餘期限的評估工具中，只有少數得到驗證。研究中找出了各種預後因素，但這些因素並未得到證實，也沒有創立任何預測工具。

結論：人口統計學的資料和臨床症狀可協助確定晚期癌症患者的剩餘生存時間。由於姑息治療的目的是盡可能維持或改善病人生活質素，所以評估工具應以方便為主，而不是加重病人的負擔。即使應用預測工具來預測病人生存期，亦不可能完全沒有錯誤。醫生應提醒患者及其家屬預測生存期的不確定性。

INTRODUCTION

Medicine is divided into three branches: diagnosis, prognosis, and treatment. Treatment was the weakest of the three areas prior to the rise of modern medicine. Since then, diagnosis and treatment have become the predominant focus of clinicians, causing prognosis to wither.[1] "How long have I got doctor?" is a difficult question often faced by physicians.[2] Evidence suggests that there are negative consequences for those who are unaware of the progression of their disease and their current status. As a result, unsatisfactory management of advanced illness can arise, leading to unnecessary hospital admissions, higher proportion of hospital deaths, absence of or late referral to palliative care services, poor symptom control, less end-of-life planning, and reduced patient choice.[3]

Patients who are terminally ill may often want to accomplish certain tasks before dying. However, predicting survival and disclosing the prognosis to patients with advanced disease is a difficult task for health care professionals. Often, patients are given an inaccurate prognosis.[2,4] Clinicians are too optimistic or too pessimistic in their predictions.[5] In 1972, Parkes[6] found little relation between actual and predicted survival in terminally ill patients. Since then, there have been developments in the care of patients with terminal cancer.[7]

Prediction of survival can help design and analyse clinical trials, allow for appropriate supportive services, guide clinical decisions, and assist in resource allocation.[4,8] Previous studies have incorporated the use of prognostic tools when determining estimations. Such tools include performance status, patient symptomatology, quality-of-life measures, or biochemical parameters.[5]

There is no single source of information to accurately provide a definitive prognosis. However, physicians may find information in the medical literature to assist in estimating survival time from patient attributes as well as their own clinical predictions.[2,8] The objective of this study was to provide an update to a previous review in 2001[5] to examine the accuracy of clinicians' prediction of survival (CPS) in terminally ill patients as well as prognostic factors of survival.

METHODS

A search was conducted using the OvidSP platform on the following databases: MEDLINE (1 January 2000 – 29 July 2012), Embase (1 January 2000 – 22 July 2012), and Cochrane Database of Systematic Reviews (1 January 2005 – July 2012). The search terms "neoplasm or cancer or tumor", "terminally ill or terminal or palliative or metastases or advanced cancer or advanced neoplasm or advanced tumor" were coupled with "clinical prediction or survival prediction or prediction of survival or prognostic tool or physician predict", "prognostic indicator or prognostic factor or prognostic predictor and survival", or "forecast and survival".

Articles that met the following criteria were included: (1) patients aged 18 years and older, and (2) the study included a range of histological diagnoses to represent those commonly seen in hospices, palliative care

programmes, and outpatient palliative oncology settings. Studies were excluded if they focused solely on utilising biochemical and molecular markers since routine blood tests are not commonly performed. This allowed for more representative systematic review for palliative care patients. A search was then conducted to identify additional articles that included relevant articles pulled from the OvidSP systematic search. Reference sections of reviews that were relevant to this study were also searched. Three of the authors independently identified articles of potential interest.

RESULTS

A total of 988 articles were identified from the search using the OvidSP platform. The titles and abstracts of the articles were manually checked to determine relevance. Articles that included only one primary cancer site, a sample population of one metastatic location, or only reported the use of biochemical markers were excluded. In the end, 85 articles were found to be relevant, some of which overlapped, examining both accuracy of clinicians' predictions and prognostic indicators of survival. As a result, 24 articles assessed the accuracy of clinicians' predictions and 71 examined prognostic factors and tools, with sample sizes ranging from 30 to 6066 patients. Accuracy of the clinicians' predictions was assessed by comparing the actual survival (AS) and estimated survival of the patients. The studies that examined the accuracy of survival predictions are summarised in Table 1.[6,7,9-30]

Table 1. Results of a literature search on clinicians' survival prediction accuracy.

Study	No. of patients	Median estimated survival (weeks)	Median survival (weeks)	Estimated survival / actual survival	Optimistic error (%)	Pessimistic error	Type of study
Parkes, 1972[6]	168	4.5	2.5	1.8	87‡	13‡	Prospective
Heyse-Moore and Johnson-Bell, 1986[7]	50	8	2	4	88	8	Prospective
Lam, 2008[9]	167	10	10.9	0.92	41.9	26.3	Prospective
Chow et al, 2005[10]	739	-	15.9	-	-	-	Retrospective
Bruera et al, 1992[11]	47	-	4 (mean)	-	-	-	Prospective
Maltoni et al, 1994[12]	100	6	5	1.2	63‡	37‡	Prospective
Maltoni et al, 1995[13]	530	-	4.6	-	-	-	Prospective
Viganò et al, 1999[14]	210	15.3	14.2	1.08	52	23	Prospective
Christakis and Lamont, 2000[15]	468	18	3.4	5.3	63	17	Prospective
Morita et al, 2001[16]	258	-	-	-	12 (estimate) 8.3 (PPI)	15 (estimate) 7.4 (PPI)	Prospective
Llobera et al, 2000[17]	200	-	36.6	-	55.1 (oncologist), 59.5 (nurses), 63.0 (family doctor)	19.2 (oncologist), 19.0 (nurses), 15.3 (family doctor)	Prospective
Hui et al, 2011[18]	151	2.0 (doctors), 2.9 (nurses)	1.7	-	-	-	Prospective
Higginson and Costantini, 2002[19]	275	42	42	1	36	22	Prospective
Evans and McCarthy, 1985[20]	42	-	-	3.17	37	9	Prospective
Kao et al, 2011[21]	50	-	29.5	-	42	26	Prospective
Selby et al, 2011[22]	1835	-	26.5	-	51	15	Prospective
Glare et al, 2004[23]	100	-	12	-	30*	43*	Prospective
Stiel et al, 2010[24]	83	-	7.1 (mean)	-	63	5	Prospective
Fromme et al, 2010[25]	429	-	-	-	27	16	Prospective
Gripp et al, 2007[26]	214	-	24.1	-	71-96†	-	Prospective
Mackillop and Quirt, 1997[27]	39	-	-	1.15	-	-	Retrospective
Addington-Hall et al, 1990[28]	1128	-	17.5	-	12	9	Retrospective
Oxenham and Cornbleet, 1998[29]	30	-	2.4	-	-	-	Prospective
Forster and Lynn, 1988[30]	108	7	3.5	2	17	1.7	Prospective

Abbreviation: PPI = Palliative Prognostic Index.

* Patients were grouped by survival interval of <1 month, >1 month, <3 months, and >3 months; the optimistic and pessimistic errors were only reported at the 3-month interval.

† Results for patients estimated to die within 1 month.

‡ Based on 100% error.

Clinicians' Prediction of Survival

Methods of obtaining CPS varied between the studies. Some clinicians estimated the survival in weeks or months.[6,7,9,11-14,16,18,30] In addition to using a temporal approach to predict patient survival in days, in some studies, clinicians were asked to determine a probabilistic estimate of survival. Table 2 demonstrates the various studies and the time intervals in which estimates were given.[6,7,9,11-27,30]

Methods of Determining Error

A variety of methods for determining error were employed between the studies. Several studies defined accuracy as the clinical prediction of survival within 33.3% of the actual survival. To calculate the error, the difference between the clinical and actual survival was divided by the actual survival and converted to a percentage. Values of <33.3% were pessimistic errors and values of >33.3% were optimistic errors.[9,15,17,18] Another prominent calculation considered serious errors to be 100% errors in either overestimating or underestimating patient survival. An optimistic prediction would be a CPS that was double the observed survival, while a pessimistic prediction would be one where the patient lived twice as long as the predicted survival.[6,12,13,30] Other methods were used by the remaining studies as summarised in Table 2.

Accuracy of Clinician Prediction

Overall, studies reported a tendency to be too optimistic in their survival predictions.[6,7,9-15,17-22,24,25,27-29] However, several studies noted a pessimistic trend in their estimates.[16,23,28]

These studies reported varying survival durations at which the clinician's estimate was most accurate. Some

Table 2. Time intervals of given estimates and error determination.

Study	Time intervals	Error determination
Parkes, 1972[6]	Estimated in weeks	100% in overestimation or underestimation
Heyse-Moore and Johnson-Bell, 1986[7]	Estimated in weeks	N/A
Lam, 2008[9]	Estimated in weeks or months	<33.3% defined as pessimistic, >33.3% defined as optimistic
Bruera et al, 1992[11]	Estimated in weeks	N/A
Maltoni et al, 1994[12]	Estimated in weeks	100% in overestimation or underestimation
Maltoni et al, 1995[13]	Estimated in weeks	100% in overestimation or underestimation
Viganò et al, 1999[14]	<2 months, 2-6 months, >6 months	N/A
Christakis and Lamont, 2000[15]	N/A	<33.3% defined as pessimistic, >33.3% defined as optimistic
Morita et al, 2001[16]	<3 weeks or <6 weeks	Difference between survival and prediction (28 days longer or shorter) and a ratio (twice or half)
Llobera et al, 2000[17]	N/A	<33.3% defined as pessimistic, >33.3% defined as optimistic
Hui et al, 2011[18]	Probability of survival ≥24 hours, 48 hours, 1 week, 2 weeks, 1 month, 3 months, and 6 months	<33.3% defined as pessimistic, >33.3% defined as optimistic Probabilistic approach: Optimistic if <30% Pessimistic if >70% Inaccurate if 40-60%
Higginson and Costantini, 2002[19]	Predicted an upper and lower estimate of survival	Falling outside minimum and maximum range
Evans and McCarthy, 1985[20]	Predicted an upper and lower estimate of survival	Falling outside minimum and maximum range
Kao et al, 2011[21]	Weeks, months, <1 year, <2 years, or >2 years	Compared prediction and survival with weighted kappa statistics
Selby et al, 2011[22]	<24 hours, 1-7 days, 1-4 weeks, 1-3 months, 3-6 months, 6-12 months, or >12 months	N/A
Glare et al, 2004[23]	<3 months, then a 2-week interval up to a maximum of 12 weeks	N/A
Stiel et al, 2010[24]	1-2 weeks, 3-4 weeks, 5-6 weeks, 7-8 weeks, 9-10 weeks, 11-12 weeks, or >12 weeks	N/A
Fromme et al, 2010[25]	≤3 days, 4 days-1 month, >1 month-6 months, or >6 months	N/A
Gripp et al, 2007[26]	<1 month, 1-6 months, or >6 months	N/A
Mackillop and Quirt, 1997[27]	0-3 months, 4-6 months, 7-12 months, 13-24 months	Ratio of median observed survival to midpoint of predicted survival interval and area under the receiver operator characteristic curves for 3-month and 1-year predictions
Forster and Lynn, 1998[30]	Weeks or months	100% in overestimation or underestimation

Abbreviation: N/A = not applicable.

articles reported significantly more accuracy in shorter survival durations. This phenomenon is known as the 'horizon effect'.[5] Higginson and Costantini[19] reported being closer to the actual survival of the patient than the maximum estimate with the average being 5 days shorter. When the minimum estimate was <2 weeks, accuracy increased to 70%.[19] Selby et al[22] concluded that predictions in the <24 hours and 1-7 days interval were more accurate if chosen ($p < 0.0001$). Fromme et al[25] noted that accuracy of survival prediction was inversely related to survival up to 6 months, declining from 85.6% for ≤3 days to 34.8%. Oxenham and Cornbleet[29] also observed more prediction accuracy in the last few days of a patients' life. On the contrary, Chow et al[10] noticed that when predicting for <12 weeks, the CPS was at least double the AS. However, the CPS estimates tended to be more accurate in the 27- to 52-week interval.

Differences among Clinicians

The CPS obtained from the studies was estimated by a variety of health care professionals. The studies exhibited discrepancy in whether different clinicians were more accurate in their predictions. Higginson and Costantini[19] reported a significant difference in accuracy between the four different palliative care team members ($p < 0.001$). Llobera et al[17] concluded that oncologists and oncology nurses showed similar prognostic ability, and primary care physicians who have less experience with terminally ill cancer patients were less accurate. Christakis and Lamont[15] commented that other non-oncology medical specialists were 3 times more likely to underestimate survival than general physicians. These authors also noted that doctors in the upper quartile of practice experience were more likely to provide an accurate prediction. Maltoni et al[12] also reported a correlation between non-experienced and experienced clinicians. In this study, the correlation coefficient varied from 0.78 ($p < 0.01$) for most experienced physicians to 0.45 ($p = 0.01$) for novices in the home care team. Hui et al[18] noted that nurses were significantly more accurate in their prediction of survival at 24 hours (91% vs 71%; $p < 0.001$) and at 48 hours (86% vs 66%; $p < 0.001$). However, the authors also observed that physicians were significantly more likely than nurses to provide accurate prediction of survival for the 6-month time point (96% vs 88%; $p = 0.006$). In contrast, a few studies also indicated no significant differences in the accuracy of predictions across the varying disciplines.[6,7,11,14,26,28]

Prognostic Indicators of Survival

A total of 71 articles investigating prognostic indicators of survival were extracted, and these are summarised in Tables 3 and 4.[11-14,16,17,20,23,24,26,28,31-90] Not all identified prognostic factors were validated. Validation can be achieved through multiple methods, with the most common being: (1) performing a test analysis on a subsample of patients, followed by a subsequent validation analysis on the remaining patients; (2) repeating the analysis on an independent sample of patients; and (3) using the 'jack-knife' or 'bootstrap' procedures of performing the same analysis repeatedly on a series of subsets from the same data set to evaluate the stability of the coefficients and the predictive ability of the model.[5] Only 21 of the articles had been validated.[13,16,31-49]

Performance status was the most prominent prognostic factor determined to be significantly indicative of survival. Of the 45 studies that determined performance status to be predictive of survival, 11 utilised the Eastern Cooperative Oncology Group (ECOG) performance status,[32,35,46,47,58-64] 15 utilised the Palliative Performance Scale (PPS),[16,39,42,48,49,65-74] and 22 utilised the Karnofsky Performance Status (KPS).[12,13,20,23,24,26,36,37,40,41,43-45,48,50-57] Martin et al[49] observed that the patient-rated performance status from the patient-generated Subjective Global Assessment was similar to the PPS in predictability of survival and could be used as an alternative. Unlike the other studies, Chan et al[68] reported that magnitude of PPS change during the disease trajectory was an indicator of survival. Yates et al[54] noted the ability of KPS scores to accurately predict short survival, although high KPS scores did not correlate significantly with longer survival.

Assessment of Clinical Predictors of Survival

Although performance status has shown a correlation with survival, several studies have determined other prognostic factors used in combination with performance status to improve prediction. Reuben et al[56] concluded that KPS, dry mouth, dyspnoea, problems with eating, weight loss, and trouble swallowing comprised the 'common terminal pathway' and reduced survival time. Due to the limited population of hospice patients from the National Hospice Study database, Viganò et al[91] explored the common terminal pathway using a population-based cohort. The authors found that loss of function, malnutrition, and asthenia characterised the common terminal pathway.

In 1998, Pirovano et al[45] updated the significant

Table 3. Results of a literature search on prognostic indicators of survival.

Study	No. of variables tested in univariate analysis	Validation	Type of study
Bruera et al, 1992[11]	14	No	Prospective
Maltoni et al, 1994[12]	N/A	Yes†	Prospective
Maltoni et al, 1995[13]	23	Yes‡	Prospective
Viganò et al, 1999[14]	42	No	Prospective
Morita et al, 2001[16]	N/A	Yes*	Prospective
Llobera et al, 2000[17]	31	No	Prospective
Evans and McCarthy, 1985[20]	N/A	Yes†	Prospective
Glare et al, 2004[23]	N/A	Yes	Prospective
Stiel et al, 2010[24]	3	No	Prospective
Gripp et al, 2007[26]	27	No	Prospective
Addington-Hall et al, 1990[28]	N/A	No	Prospective
Ohde et al, 2011[31]	48	Yes	Prospective
Feliu et al, 2011[32]	43	Yes	Prospective
Hyodo et al, 2010[33]	N/A	Yes	Prospective
Toscani et al, 2005[34]	36	Yes	Prospective
Chuang et al, 2004[35]	30	Yes*	Prospective
Zhou et al, 2009[36]	34	Yes*	Retrospective
Chow et al, 2008[37]	N/A	Yes	Prospective
Teunissen et al, 2006[38]	49	Yes	Prospective
Stone et al, 2008[39]	N/A	Yes	Prospective
Chow et al, 2009[40]	16	Yes*	Retrospective
Scarpi et al, 2011[41]	N/A	Yes	Retrospective
Morita et al, 1999[42]	22	Yes*	Retrospective
Chow et al, 2011[43]	N/A	Yes	Retrospective
Durand et al, 2012[44]	11	Yes*	Prospective
Pirovano et al, 1999[45]	36	Yes	Prospective
Sloan et al, 2001[46]	N/A	Yes	Prospective
Chiang et al, 2010[47]	22	Yes*	Prospective
Tarumi et al, 2011[48]	7	Yes	Prospective
Martin et al, 2010[49]	25	Yes	Prospective
Chang and Lin, 2009[50]	21	No	Prospective
Lam et al, 2007[51]	28	No	Prospective
Caraceni et al, 2000[52]	41	No	Prospective
Hwang et al, 2004[53]	12	No	Retrospective
Yates et al, 1980[54]	N/A	Yes†	Retrospective
Mor et al, 1984[55]	N/A	Yes†	Prospective
Reuben et al, 1988[56]	16	No	Retrospective
Barbot et al, 2008[57]	13	No	Prospective
Suh et al, 2010[58]	17	No	Prospective
Bachelot et al, 2000[59]	9	No	Retrospective
Kao et al, 2009[60]	23	No	Prospective
Rosenthal et al, 1993[61]	19	No	Prospective
Allard et al, 1995[62]	N/A	No	Prospective
Coates et al, 1997[63]	N/A	No	Prospective
Walsh et al, 2002[64]	41	No	Prospective
de Miguel Sánchez et al, 2006[65]	29	No	Prospective
Weng et al, 2009[66]	N/A	No	Retrospective
Head et al, 2005[67]	N/A	N/A†	Retrospective
Chan et al, 2013[68]	4	No	Prospective
Alshemmari et al, 2012[69]	N/A	No	Prospective
Lau et al, 2006[70]	4	No	Retrospective
Lau et al, 2009[71]	6	No	Retrospective
Lau et al, 2009[72]	6	No	Retrospective
Morita et al, 1999[73]	22	Yes*	Retrospective
Younis et al, 2009[74]	18	No	Retrospective
Yun et al, 2001[75]	27	No	Prospective
Schonwetter et al, 1990[76]	N/A	No	Retrospective
Viganó et al, 2000[77]	56	No	Prospective
Hardy et al, 1994[78]	11	No	Prospective
Shadbolt et al, 2002[79]	25	No	Prospective
Vigano et al, 2004[80]	33 (cohort 1), 20 (cohort 2)	No	Prospective
Park et al, 2006[81]	17	No	Prospective
Tamburini et al, 1996[82]	N/A	No	Prospective
Lloyd-Williams et al, 2009[83]	8	No	Prospective
Caruso et al, 2010[84]	16	No	Retrospective
Cuervo Pinna et al, 2009[85]	N/A	No	Retrospective
Vitetta et al, 2001[86]	N/A	No	Retrospective
Cheung et al, 2009[87]	N/A	No	Retrospective
Ventafridda et al, 1990[88]	N/A	No	Prospective
Zeng et al, 2011[89]	9	No	Retrospective
Tsamandouraki et al, 1992[90]	N/A	No	Prospective

Abbreviation: N/A = not available.

* Subsequently validated in training / testing set.

† Subsequently validated in other studies.

‡ Subsequently validated in later series.

Table 4. Prognostic factors indicative of survival.

Study	No. of patients	Prognostic factor
Bruera et al, 1992[11]	47	Dysphagia, cognitive failure, weight loss
Maltoni et al, 1994[12]	100	KPS
Maltoni et al, 1995[13]	530	CPS, anorexia, dysphagia, palliative steroid treatment, KPS, hospitalisation
Viganò et al, 1999[14]	248	Loss of function, malnutrition, asthenia
Morita et al, 2001[16]	245	PPI (PPS, oral intake, oedema, dyspnoea, delirium)
Llobera et al, 2000[17]	200	Asthenia, predicted survival by oncologist, Hebrew Rehabilitation Centre for Aged Quality of Life Index
Evans and McCarthy, 1985[20]	42	KPS correlated better with actual survival than did clinical predictions
Glare et al, 2004[23]	100	PaP (dyspnoea, anorexia, KPS, CPS, white blood cell count, lymphocyte %)
Stiel et al, 2010[24]	83	PPI and PaP not able to produce precise reliable prognosis for individual patients
Gripp et al, 2007[26]	216	Primary cancer (colorectal and breast) favourable, brain metastases, KPS <50%, strong analgesics, dyspnoea, LDH, leukocytosis
Addington-Hall et al, 1990[28]	230	Spitzer Quality of Life Index score: low score correlated with likeliness to die within 6 months compared with higher scores
Ohde et al, 2011[31]	158	Anorexia, dyspnoea, oedema, BUN >25.0 mg/dl, platelets <260,000/mm^3
Feliu et al, 2011[32]	880	ECOG performance status, LDH levels, lymphocyte levels, albumin levels, and time from initial diagnosis to diagnosis of terminal disease
Hyodo et al, 2010[33]	409	Japan Palliative Oncology Study–Prognostic Index (CPS, consciousness, pleural effusion, white blood cell count, and lymphocyte %)
Toscani et al, 2005[34]	574	Dyspnoea, cachexia, Katz Index of Independence in Activities of Daily Living, oliguria, fatigue, physical symptom index
Chuang et al, 2004[35]	539	Lung metastasis, liver metastasis, tiredness, ascites, oedema, cognitive impairment, weight loss, ECOG performance status
Zhou et al, 2009[36]	1019	Weight loss, nausea, dysphagia, dyspnoea, oedema, cachexia, dehydration, sex, KPS, and quality of life
Chow et al, 2008[37]	1307	Primary cancer site, site of metastases, KPS
Teunissen et al, 2006[38]	181	Nausea, dysphagia, dyspnoea, confusion, absence of depression
Stone et al, 2008[39]	201	PPI (PPS, oral intake, oedema, dyspnoea, delirium)
Chow et al, 2009[40]	1308	KPS, sites of metastases
Scarpi et al, 2011[41]	361	PaP with delirium
Morita et al, 1999[42]	245	Performance status, oedema, dyspnoea at rest, delirium
Chow et al, 2011[43]	908	Primary cancer site, site of metastases, KPS, fatigue, appetite, shortness of breath
Durand et al, 2012[44]	500	Cochin Risk Index Score ≥7, urea >12 mmol/l, KPS ≤30%, leukocytes >15 g/l, transthyretin ≤0.05 g/l, male sex
Pirovano et al, 1999[45]	451	PaP (dyspnoea, anorexia, KPS, CPS, total white blood cell count, lymphocyte %)
Sloan et al, 2001[46]	1560	Good/Bad/Uncertain index (performance status, CPS, patient-reported KPS, patient-reported appetite)
Chiang et al, 2010[47]	727	ECOG performance status, grade 3 oedema, muscle power, heart rate, respiratory rate, intervention tube, sex, haemoglobin, BUN, and serum glutamic pyruvate transaminase
Tarumi et al, 2011[48]	958	Age, PPS, PaP (dyspnoea, anorexia, KPS, CPS, total white blood cell count, lymphocyte %)
Martin et al, 2010[49]	1767	Disease site, performance status (patient-rated and PPS), % weight change*, food intake*, dysphagia*
Chang and Lin, 2009[50]	180	Sex, KPS, and Taiwanese version of the MD Anderson Symptom Inventory total score
Lam et al, 2007[51]	170	Age, number of metastatic sites, serum albumin, KPS, Edmonton Symptom Assessment System score
Caraceni et al, 2000[52]	393	Delirium and PaP
Hwang et al, 2004[53]	429	KPS, quality of life, physical symptom distress score
Yates et al, 1980[54]	104	Low KPS score
Mor et al, 1984[55]	685	KPS
Reuben et al, 1988[56]	1592	KPS, dry mouth, shortness of breath, problems with eating, weight loss, trouble swallowing
Barbot et al, 2008[57]	177	KPS, number of metastatic sites, low serum albumin, LDH concentration
Suh et al, 2010[58]	209	Objective prognostic score (resting dyspnoea, low ECOG performance status = 4, leukocytosis >11,000/mm^3, elevated bilirubin >2.0 mg/dl, elevated creatinine ≥1.5 mg/dl, elevated LDH ≥502 IU/l, reduced oral intake)
Bachelot et al, 2000[59]	144	LDH >600 IU, ECOG performance status (2 or 3)
Kao et al, 2009[60]	459	Liver cancer, systolic blood pressure, heart rate, haemoglobin, BUN, ECOG performance status, extremity muscle power, and male sex
Rosenthal et al, 1993[61]	148	Poor ECOG performance status (3-4), admission at first referral to palliative care service, hyperbilirubinemia >19 μmol/l, hypotension (systolic blood pressure <90 mm Hg)
Allard et al, 1995[62]	1081	Poor ECOG performance status = 4

Abbreviations: BUN = blood urea nitrogen; CPS = clinician prediction of survival; ECOG = Eastern Cooperative Oncology Group; KPS = Karnofsky Performance Status; LDH = lactate dehydrogenase; PaP = Palliative Prognostic Score; PPI = Palliative Prognostic Index; PPS = Palliative Performance Scale.

Table 4. (cont'd)

Study	No. of patients	Prognostic factor
Coates et al, 1997[63]	735	Age, ECOG performance status, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire–Core 36 (overall physical condition, overall quality of life, global functioning, and social functioning)
Walsh et al, 2002[64]	954	Sex, poor ECOG performance status, dysphagia, early satiety
de Miguel Sánchez et al, 2006[65]	98	PPS, heart rate, respiratory rate
Weng et al, 2009[66]	492	Lower PPS, older age, male sex
Head et al, 2005[67]	396	PPS
Chan et al, 2013[68]	400	Magnitude of PPS change during disease trajectory
Alshemmari et al, 2012[69]	91	PPI (PPS, oral intake, oedema, dyspnoea, delirium)
Lau et al, 2006[70]	733	Initial PPS score, age, sex
Lau et al, 2009[71]	513	Initial PPS score, age, diagnosis, cancer type and site
Lau et al, 2009[72]	6066	Initial PPS score, age, sex, location, diagnosis
Morita et al, 1999[73]	245	PPI (PPS, appetite loss, oedema, dyspnoea at rest, delirium)
Younis et al, 2009[74]	180	PPS, sex
Yun et al, 2001[75]	91	Terminal Cancer Prognostic Score (severe anorexia, diarrhoea, mild confusion)
Schonwetter et al, 1990[76]	172	Dressing ability, pulse rate, level of appetite, transferring ability
Viganó et al, 2000[77]	227	Primary lung cancer, presence of liver metastases, amount of weight loss (>8.1 kg within 6 months), LDH >681 U/l, serum albumin <35 g/l, lymphocyte count <1 x 10^9/l, nausea and vomiting intensity, moderate-to-severe comorbidity (vs absent-to-mild), CPS <2 months (vs 2-6 and >6 months)
Hardy et al, 1994[78]	107	CPS, lung primary, intervention, dyspnoea, and decubitus ulcers
Shadbolt et al, 2002[79]	181	Self-rated health, appetite loss, emotional functioning, fatigue, diagnosis type, treatment
Vigano et al, 2004[80]	1006	Physical health-related quality-of-life factors (nausea, emesis, dyspnoea weakness)
Park et al, 2006[81]	142	European Quality of Life–5 Dimensions
Tamburini et al, 1996[82]	115	Confusion, cognitive status, global health status
Lloyd-Williams et al, 2009[83]	90	Depression, breathlessness, tiredness
Caruso et al, 2010[84]	83	Thrombocytopenia, Simplified Acute Physiology Score
Cuervo Pinna et al, 2009[85]	195	Prevalent dyspnoea
Vitetta et al, 2001[86]	102	Pain, dyspnoea, immobility, and adjusted Charlson comorbidity scores
Cheung et al, 2009[87]	198	Lack of appetite, drowsiness, dyspnoea, and fatigue
Ventafridda et al, 1990[88]	120	Appearance of unendurable symptoms and aggravation of previous controllable symptoms (dyspnoea, pain, delirium, vomiting)
Zeng et al, 2011[89]	808	Deterioration of global Edmonton Symptom Assessment System symptoms (pain, tiredness, nausea, depression, anxiety, drowsiness, appetite, well-being, dyspnoea)
Tsamandouraki et al, 1992[90]	202	Home care less effective compared with hospital care

Abbreviations: BUN = blood urea nitrogen; CPS = clinician prediction of survival; ECOG = Eastern Cooperative Oncology Group; KPS = Karnofsky Performance Status; LDH = lactate dehydrogenase; PaP = Palliative Prognostic Score; PPI = Palliative Prognostic Index; PPS = Palliative Performance Scale.

* Significant in multivariable analysis, but did not further improve predictive accuracy.

prognostic factors from an earlier study[13] with the addition of biochemical parameters. The earlier study concluded that significant clinical predictors of survival were anorexia, dyspnoea, palliative steroid therapy, KPS score, and hospitalisation.[13] In the update, the group developed an assessment tool from an initial 36 variables using a backward selection procedure. As a result, the Palliative Prognostic Score (PaP Score) was constructed based on the following variables: clinical prediction of survival, KPS, anorexia, dyspnoea, total white blood cell count, and lymphocyte percentage. A numerical score was assigned to each variable based on the prognostic significance shown by each category in the multivariate analysis. The sum of the single scores gave the overall PaP Score for each patient, and was used to subdivide the study population into three groups with different probabilities of survival at 30 days — group A: probability of survival at 30 days of >70%, with patient score of ≤5.5; group B: probability of survival at 30 days of 30-70%, with patient score of 5.6-11.0; and group C: probability of survival at 30 days of <30%, with patient score of >11.0. The PaP Score based on clinical and biochemical variables was statistically significant in a multivariate analysis, and validated in the training set and in an independent case series.[92] Glare et al[23] reported that the PaP Score was able to accurately identify three prognostic groups within advanced cancer patients under the care of an

oncologist. Tarumi et al[48] validated the PaP Score in patients referred to a palliative care consultation service at a Canadian acute care hospital where age, PPS, and PaP Score remained significantly associated with survival.

Caraceni et al[52] evaluated the impact of delirium on the survival of advanced cancer patients who were also assessed by using the PaP score. Delirium was found to significantly worsen the life expectancy associated with the PaP Score. Patients with delirium had a different survival curve when compared with non-delirious patients ($p < 0.0001$). This result suggested that assessing cognitive status and utilising the PaP Score could increase accuracy in >70% of patients when predicting 30-day survival.[52] Scarpi et al[41] also reported delirium to be statistically significant ($p < 0.001$) and therefore revised the PaP Score to incorporate delirium (D-PaP Score). This prognostic tool was retrospectively tested on the sample population from Caraceni et al[52] and determined to have a better overall performance than the PaP Score.[41]

Morita et al[42] developed and validated a simple indicator for survival of <3 weeks or <6 weeks based on the presence of clinical symptoms. Risk factors were identified by multiple logistic regressions with a reported sensitivity and specificity of >70%. Since scoring methods were suggested to be more effective than prediction based on the presence of certain clinical symptoms, this same group went on to develop and subsequently validate a scoring system using the same patient population.[73] The Palliative Prognostic Index (PPI) evaluates performance status, oral intake, oedema, dyspnoea at rest, and delirium. In the training set, patients were classified into three groups — group A: PPI ≤2.0); group B: 2.0< PPI ≤4.0; and group C: PPI >4.0). When a PPI of >6.0 was adopted as a cut-off point, 3-week survival was predicted with a sensitivity of 80% and specificity of 85%. When a PPI of >4.0 was used as a cut-off, 6-week survival was predicted with a sensitivity of 80% and a specificity of 77%. The PPI was able to predict whether patients lived longer than 3 or 6 weeks.[73] In a later study, this group of authors compared the PPI with physician-predicted survivals.[16] The PPI was able to improve physicians' CPS, decreasing serious error from 27% to 16% ($p = 0.028$). Stone et al[39] validated the PPI with patients referred to a hospital-based consultancy palliative care service, a hospice home care service, and a hospice inpatient unit, and who were also receiving palliative chemotherapy or radiotherapy. Alshemmari et al[69] reported that the PPI may be helpful for oncologists in predicting survival and in-hospital mortality of patients with advanced cancer in the acute care setting.

Durand et al[44] constructed a different model consisting of urea >12 mmol/l, KPS <30%, leukocytes >15 g/l, transthyretin <0.05 g/l, and male sex to predict 2-week survival. A Cochin Risk Index Score of <7 identified high-risk patients resulting in a positive predictive value of 78% in the validation set.

Sloan et al[46] produced a simple stratification factor for phase III oncology clinical trials involving patients with advanced malignant disease known as the Good/Bad/Uncertain (GBU) index. This index is based on CPS, performance status, patient-reported KPS score, and patient-rated appetite. Patients were classified as having a relatively good prognosis if three or more items showed a positive indication, a bad prognosis if three or more were negative, and an uncertain prognosis otherwise. The results of this study showed that the GBU index was able to improve the prognostic power of a Cox model quartile index and performance status alone, increasing the accuracy of survival classification estimates by 5 to 10%. For patients with performance status of 0 or 1, significant survival patterns existed between GBU groups ($p = 0.002$ and 0.0001, respectively).

Suh et al[58] constructed an objective prognostic score that also incorporated performance status. Based on multivariate analysis, reduced oral intake, resting dyspnoea, low performance status, leukocytosis, elevated bilirubin, elevated creatinine, and elevated lactate dehydrogenase (LDH) were associated with poor prognosis. The objective prognostic score range is 0.0 to 7.0. For a cut-off score of 3.0, the 3-week prediction sensitivity is 74.7%, specificity is 76.5%, and overall accuracy is 75.5%. The instrument was able to demonstrate accurate prediction of 3-week survival in the training set, although it was not validated in an independent population.

Chuang et al[35] developed a prognostic scale based on multivariate analysis that reported liver and lung metastases, ECOG performance status, weight loss, oedema, cognitive impairment, tiredness, and ascites to be independently associated with shorter survival. The scale ranged from 0.0 to 8.5. For scores of <3.5, 2-week survival was predicted with 0.72 and 0.61 accuracy for

the training and testing sets, respectively, and for scores of <6.0, 1-week survival was predicted with 0.72 and 0.66 accuracy, respectively.

Chow et al[37] constructed a three-variable model for patients with metastatic cancer attending a palliative radiotherapy clinic using the readily available parameters of primary cancer site, site of metastases, and KPS. Each factor was assigned a value proportional to its prognostic weight and weighted scores for each patient were summed to obtain a survival prediction score. Patients were also grouped according to the number of risk factors (NRF): non–breast cancer, metastases other than bone, and KPS ≤60. The model was subsequently validated in temporal and external data sets, and the three-variable NRF model was preferred because of its relative simplicity. The same model was again validated using Radiation Therapy and Oncology Group (RTOG) 9714 data comprising patients treated at multiple institutions.[43] The NRF method was able to distinguish intermediate-risk patients that the survival prediction score method classified into a low-risk group, yielding a statistically significant difference in survival estimates of the two groups ($p < 0.0001$).[43] Chow et al[40] also constructed a predictive model for patients referred to the Rapid Response Radiotherapy Program using recursive partitioning. Sixteen factors characterising patients with metastases at first referral were analysed. The model was able to separate patients into three groups with different survival durations, as follows: KPS >60, KPS <60 with bone metastases only, and KPS <60 with other metastases. The model was then validated temporally and externally, but only performed moderately well. There was no advantage to this model compared with the previous survival prediction score and NRF prognostic models.

Chiang et al[47] proposed a computer-assisted estimated probability formula for predicting death within 7 days of hospice admission in terminal cancer patients. This formula incorporated demographic, clinical, and laboratory data. The formula evaluated ECOG performance status, grade 3 oedema, muscle power, heart rate, respiratory rate, intervention tube, sex, haemoglobin, blood urea nitrogen, and serum glutamic pyruvate transaminase. This model exhibited an 82.3% accuracy when comparing using receiver operating characteristic curves.

Feliu et al[32] developed a prognostic nomogram for terminal cancer patients based on five clinical and laboratory variables to estimate probability of survival at 15, 30, and 60 days. The instrument was validated and calibrated with an external cohort. ECOG performance status, LDH, albumin levels, lymphocyte levels, and time from initial diagnosis to diagnosis of terminal disease were included in the multivariable Cox proportional hazard as prognostic factors of survival. These factors formed the nomogram and showed high predictive performance with a bootstrapped corrected concordance of 0.70 and an external independent validation of 68% accuracy.

Zhou et al[36] developed a simple Chinese Prognostic Scale (ChPS) for predicting survival in 1019 advanced cancer patients divided into two sets using stratified random sampling to obtain a 'training set' for developing the scale and a 'testing set' for validation. A total of 10 prognostic factors were determined: weight loss, nausea, dysphagia, dyspnoea, oedema, cachexia, dehydration, sex, KPS, and quality of life. The ChPS score was calculated by summing the partial scores of the prognostic factors from 0 (no altered variables) to 124 (maximal altered variables). The score cut-off point of 3 months' survival was 28. Patients with scores of >28 usually lived for <3 months. The training set had an accuracy of 69.4%, while the validation set had 65.4% accuracy.

Three models were constructed without the use of performance status to aid in estimated patient survival.[31,33,75] Ohde et al[31] developed a prognostic prediction model for 2-week survival among patients with terminal cancer in a palliative care unit. A prognostic model with a total of 8 points was constructed, as follows: 2 points each for anorexia, dyspnoea, and oedema; 1 point each for blood urea nitrogen >25 mg/dl and platelets <260,000/mm^3. Bootstrapped validation beta coefficients were similar to the original cohort beta coefficients. When total scores were 0-1 point, 2-3 points, 4-5 points, or >6 points, 2-week mortality rates were 7.7%, 19.4%, 59.3%, and 100% respectively. This model has yet to be externally validated.

Hyodo et al[33] studied 32 clinical predictors to develop a new tool, the Japan Palliative Oncology Study–Prognostic Index, using the Cox proportional hazard model. Five significant predictors were included: CPS, consciousness, pleural effusion, white blood cell count, and lymphocyte percentage were used to divide the patients into three risk groups: low (group

A), intermediate (group B), and high (group C). The probability for survival of >30 days for groups A, B, and C were 78%, 61%, and 16%, respectively. The validation set yielded consistent results (81%, 48%, and 11% for groups A, B, and C, respectively).

Yun et al[75] developed the Terminal Cancer Prognostic (TCP) score, a prognostic index for terminal cancer patients. After adjusting for primary tumour site, three predictors were negative predictors of survival: anorexia, severe diarrhoea, and mild confusion. The tool ranged from a score of 0 (none of the variables) to 7 (all variables) with 2 points for anorexia, 3 for diarrhoea, and 2 for confusion. The TCP score was proved to have a strong association with survival.

Rosenthal et al[61] also reported certain clinical and laboratory data to be significantly associated with shorter survival. This group reported poor ECOG performance status (3-4), admission at first referral to palliative care service, hyperbilirubinemia (>19 μmol/l), and hypotension (systolic blood pressure, <90 mm Hg) as indicators. Bachelot et al[59] only found laboratory data in combination with performance status to be significant. These authors noted LDH of >600 IU and ECOG performance status 2 or 3 to be predictive of survival.

In combination with performance, few studies found survival to be related to the type of primary cancer.[26,49,60,65,71,76,78] Gripp et al[26] determined colorectal and breast cancer had a favourable prognosis, whereas brain metastasis was associated with a poor prognosis. Kao et al[60] reported shorter survival among patients diagnosed with liver cancer. Hardy et al[78] determined that a lung primary was associated with survival prediction. Lau et al[71] reported initial PPS score, age, diagnosis, cancer type, and site to be prognostic factors associated with shorter survival. These researchers went on to find initial PPS score, age, diagnosis, sex, and location that the PPS was recorded to be significant predictors of survival time.[72] Two other studies also found sex to be indicative of survival.[66,74] Weng et al[66] found PPS, age, and sex to be predictive of shorter survival. Younis et al[74] reported survival to be correlated with only PPS and sex. Other studies have found the number of metastatic sites rather than the type of primary site to be prognostic of survival.[51,57]

Application of physical indicators has been suggested, but different assessment tools were used to assess these factors. Many studies also showed a relationship between survival and other quality-of-life components or symptoms, most of which reported performance status as affecting duration of survival.[17,28,50,53,63,64,81] Other studies have concluded certain quality-of-life symptoms to be significant, but not performance status.[11,34,38,80,82-84,88,89] Ventafridda et al[88] noted appearance of unendurable symptoms and aggravation of previous controllable symptoms in 97% of patients within 1 week of death and >50% of patients in the last 24 hours. As the 'unendurable' and 'difficult to control' symptoms were not specifically or clearly defined, this study had limited clinical applicability.[5] Similarly, Zeng et al[89] reported a significant deterioration of global Edmonton Symptom Assessment System (ESAS) symptoms within the last 4 weeks prior to death compared with the scores in previous months. At 1 week prior to death, the worst ESAS symptoms were fatigue, appetite, and well-being. Tsamandouraki et al[90] noted that although the quality of life of patients cared for at home was superior to that of patients in hospital, home care was less effective when survival was the only outcome criterion.

The presence of dyspnoea was noted in a few studies as an indication of patient survival.[85-87] Cuervo Pinna et al[85] found that patients with incident dyspnoea had higher average survival duration than those with prevalent dyspnoea. Vitetta et al[86] also described dyspnoea as having a negative effect on survival, along with pain, immobility, and adjusted Charlson comorbidity score. Cheung et al[87] noticed lack of appetite, drowsiness, dyspnoea, and fatigue to be independent prognostic factors.

DISCUSSION

CPS was determined to be correlated with survival in a few of the studies reviewed,[13,17,23,33,41,45,46,48,52,77] however, predictions tended to be too optimistic.[6,7,9-15,17-22,24,25,27-29] In a study comparing physician behaviour in disclosing prognostic expectations, Lamont and Christakis[93] found that physicians provided frank survival estimates only 37% of the time and knowingly inaccurate estimates 40.3% of the time, tending to be more optimistic than the formulated predictions. Disinterested doctors with little time to get to know a patient may be able to provide a more accurate prognosis.[26] Experience with terminal cancer may help to improve the ability to predict survival. Llobera et al[17] found oncology nurses and oncologists to have similar prognostic ability compared with primary care physicians who are less

experienced in caring for terminally ill patients. Nurses, who had more experience at a patient's bedside than physicians and therefore were better able to pick up imminent signs of death, showed a higher accuracy when predicting the last 24 hours of life.[18]

Although physicians incorrectly predict survival, the fact that predictions are correlated with survival indicates that they are able to sense when things are going wrong.[94] The results suggest that clinicians are able to separate patients into classes, although they may be poorly calibrated due to the inability to assign meaningful probabilities to outcomes.[94]

Inaccurate predictions have been reported to have negative effects.[5] Optimistic life expectancy can cause patients to be denied eligibility for services to improve their quality of dying, while erroneously pessimistic results may negatively impact the financial status of hospice programmes by leading to provision of uncompensated care for patients who live longer than 6 months.[95] Palliative care requires a patient-oriented active approach. An important step in preventing adverse consequences of an incorrect prognosis is to be aware of possible incomplete diagnostics.[96] If doctors are able to better anticipate death, medical treatments and use of palliative care can be optimised, allowing patients to avoid unnecessary treatments near the end of life.[94]

The prevalence of similar symptoms among patients with varying primary and metastatic sites supports the existence of a common final clinical pathway or 'terminal common pathway' in patients with advanced cancer.[56] To better assess survival duration, many assessment tools have been developed and validated. The instruments have a range of prognostic factors, containing a varying combination of demographic data, symptoms, and laboratory data. The differences may be due to the varying purposes and outcomes of the study. For example, Chow et al[37] used readily available parameters to construct a three-variable model. Also, the requirements for inclusion in sample populations were different for each study, potentially influencing the outcome as noted by Viganò et al.[91]

Depression as a prognostic factor resulted in contradicting opinions. Teunissen et al[38] found the absence of depression to be indicative of survival, whereas Lloyd-Williams et al[83] reported the presence of depression to be prognostic. Teunissen et al[38] suggested that the depression and cancer progression relationship resulted from the use of questionnaires rather than from psychiatric (Diagnostic and Statistical Manual of Mental Disorders) criteria. The associations may be reflective of symptoms mimicking depression, but are in fact markers of tumour burden or cancer progression.[38]

Treatment for patients with terminal cancer shifts from curative to palliative, focusing on relieving symptoms and managing complications.[97] Many studies have determined the prognostic value of biochemical parameters in palliative care. However, since the goal of care is to relieve pain and maintain quality of life, routine blood tests are avoided.[5] Assessment tools should be convenient in order to reduce the burden on terminally ill cancer patients, therefore, instruments that rely on demographic information or clinical symptoms should be emphasised.

The absence of optimistic errors cannot be avoided due to the nature of terminal cancer.[16] The clinical value of individual prognostication is limited, even with the use of an assessment tool as shown by Morita et al.[16] Clinicians should inform patients and their friends and family of the uncertainty in survival prediction.

Limitations

Due to the heterogeneity of the patient populations used in the studies, it is difficult to draw a conclusion on which clinical symptoms are predictors for survival. Many of the studies that determine prognosis factors for survival did not subsequently undergo validation. Future studies should compare the different assessment tools using the same patient population in order to better assess the validity and outcome of each for terminally ill cancer patients.

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DECLARATION

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