External Validation of the Number of Risk Factors Score in a Palliative Care Outpatient Clinic at a Comprehensive Cancer Center

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Abstract

Background: Prognostic tools are available to predict if terminally ill cancer patients have days or weeks to live. Tools for predicting the prognosis in ambulatory patients at an earlier stage are lacking. The Number of Risk Factors (NRF) score developed in ambulatory cancer patients receiving palliative radiation therapy may be suitable for this purpose but has not been tested in a palliative care setting.

Objective: Our aim was to evaluate the prognostic accuracy of the NRF score in patients referred to a palliative care outpatient clinic at a comprehensive cancer center.

Methods: We conducted a retrospective chart review of NRF scores and survival in 300 consecutive, newly referred patients. Measurements included primary cancer type, extent of disease, Karnofsky Performance Scale (KPS) score, and survival duration after first visit. One point was allocated each for cancer other than breast cancer, metastases other than bone, and low KPS score.

Results: Of 300 patients, 236 (79%) had advanced disease. Of those 236, 212 (90%) had a cancer other than breast cancer, 180 (76%) had metastatic disease in sites other than bone, and 64 (27%) had a KPS score < 70%. During the 2-year follow-up, 221 (94%) patients died, with overall median survival of 4.9 months (95% confidence interval, 3.9–6.1 months). NRF scores of 0 to 1, 2, and 3 split the sample into subgroups with highly significantly different survival among the groups, with medians 9.0, 4.6, and 2.1 months, respectively (Wilcoxon test $\chi^2 = 43.9$, degrees of freedom [df] 2, $p < 0.0001$). A simple parametric model was fit to determine the probability of subgroup members surviving to a certain number of months.

Conclusions: In cancer patients referred to palliative care earlier in their disease trajectory, the NRF score may be a useful prognostic tool. Further validation in other palliative care populations is needed.

Introduction

ACCURATELY PREDICTING SURVIVAL is an important clinical skill for palliative care clinicians to be competent in, but this can be a very challenging task.¹ Several tools have been developed over the past 10 to 15 years to aid the clinician in formulating a prognosis, including the Palliative Prognostic Index (PPI), the Palliative Prognostic (PaP) Score, and the Prognosis in Palliative care Study (PiPS) model.^{2–4} However, these models were all developed in patients with far-advanced disease, usually on hospice care, in whom survival is short and typically measured in days to weeks. These tools predict survival at 3 and 6 weeks in the case of the PPI,² 1 month in the case of PaP Score,⁵ and 2 weeks and 2 months in the case of the PiPS model.⁴ None of these tools is therefore very suitable for ambulatory patients referred to

palliative care outpatient clinics earlier in the disease trajectory when the prognosis is likely to be measured in many months or even years,⁶ impacting on decisions such as having further chemotherapy, undergoing aggressive palliative interventions such as surgeries, or life choices such as continuing to work or a much more timely referral to hospice.

Long-range prognostic information is available in the oncology literature for individual cancers,^{7–10} but these data are not easy to access. Even when they are located, they focus on the impact of specific chemotherapeutic regimens or other anticancer treatments on the recurrence of disease and survival. These disease-specific data are not so helpful in a palliative care clinic where the population is very heterogeneous with regard to tumor type and treatment.

Prognostication in ambulatory patients with advanced disease who are heterogeneous for cancer type is also a

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clinical challenge for radiation oncologists delivering palliative radiation therapy. Within that setting, a survival model was developed in the past decade.¹¹ Named the Predictive Model for Survival in Patients with of Advanced Cancer, the original version consisted of six factors: primary cancer site, site of metastases, Karnofsky Performance Score (KPS), and the three symptoms of fatigue, appetite, and shortness of breath. The three symptoms are scored using the Edmonton Symptom Assessment Scale (ESAS). This model was able to categorize patients into three subgroups with median survivals of 3, 6, and 12 months. Because subjective patient-reported outcomes such as symptom scores are potentially problematic as predictive factors in a prognostic model, the six-variable model was subsequently compressed to a model containing just the three physician-measured ones (primary site, metastases, and performance status), with performance dichotomized into good (KPS score 70 or above) or poor (KPS score below 70). When the two models were compared, no significant differences in predictive ability was found between them.¹²

The three-variable model has been evaluated with both weighted and unweighted values for each of its variables. The weighted version was called the Simple Prognostic Score (SPS), and the unweighted version called the Number of Risk Factors (NRF) model. The ability of the SPS and NRF model to separate patients into three prognostic groups was similar. Because there were no differences in the prognostic accuracy of any of these versions of the Predictive Model for Survival in Patients with of Advanced Cancer and because a simple, valid, objective prognostic model is urgently needed for palliative care outpatient practice, the aim of this study was to test the validity of the simplest version of these models—the NRF—in ambulatory patients attending a palliative care outpatient clinic at a comprehensive cancer center.

Methods

Study design

This was a retrospective chart review of 300 consecutive patients referred to one pain and palliative care clinic at Memorial Sloan-Kettering Cancer Center in New York, New York, from the beginning of December 2008 to the end of April 2010. Typical patients in this clinic have advanced cancer but a good performance status and are on anticancer treatment. They are primarily referred by their treating oncologist because they have high-risk factors for poor pain control. A waiver was obtained from the institutional review board to use existing data, and written informed consent was not required.

Participants

Patients' charts were included for review if they were aged 18 years or older, had a proven diagnosis of cancer, and had advanced disease (locally advanced or metastatic). Patients receiving adjuvant therapy and cancer survivors were not included. There were no other inclusion or exclusion criteria. Patients were at different stages of treatment and may or may not have been receiving anticancer therapy (see Table 1).

Study measures

Clinical and demographic information on the patients was obtained from their charts. The information on the primary

TABLE 1. PATIENT CHARACTERISTICS, N = 237

	N	%
Sex		
Male	102	43%
Female	135	57%
Age, years		
Median		59
Range		21–87
Primary cancer site		
Lung	26	11%
Breast	24	10%
Prostate	9	4%
Other	178	75%
Sites of metastases		
Bone only	26	11%
Other	182	77%
Karnofsky Performance Score		
10–20	0	0%
30–40	5	2%
50–60	60	25%
70–80	132	56%
90–100	40	17%
Median		80
Range		30–90

cancer site, site of metastases, and performance status was obtained from the consultation note made at the first visit with the palliative medicine physician. These data were used to calculate the score for the NRF model by assigning one point for any primary cancer site other than breast cancer, one point for metastases other than bone (lymph nodes were arbitrarily included as nonosseous metastatic disease, even if they were regional, and were allocated one point; locally advanced disease without known metastases was not allocated a point), and one point for a KPS score < 70. Survival was measured in days, starting from the date of the first consultation with the palliative medicine physician. The date of death was obtained from the institutional database, which obtains information on the dates of death from notifications by staff of the cancer center as well as from regular updates from the Social Security Death Index.

Statistical considerations

Patients' charts were retrospectively reviewed for the variables relating to the NRF model, using the KPS score documented by the palliative medicine physician at the first visit. The points were then allocated and totaled for each patient to provide the NRF score. Patients who were not known to have died at the end of the follow-up period (April 30, 2012) were censored at the date of their last visit to the cancer center. Survival analysis was performed according to four categories, based on the NRF scores (0, 1, 2, or 3). The Kaplan Meier product-limit method was used to compute survival curves for patients grouped according to NRF score. Based on the shapes of the survival curves that were obtained, the Wilcoxon-Gehan test was used for the overall comparison among the NRF scores for groups and pair-wise comparisons between the groups. A parametric model of the survival distributions was fit using SAS Proc Lifereg (SAS version 9.3, SAS Institute, Cary, NC). This facilitated calculating a

simple predictive formula for survival within each NRF score subgroup. When evaluating the model's predictive accuracy at the individual patient level, groups 0 and 1 were collapsed together because of the small numbers scoring zero. *P* values were considered to be significant if <0.05 .

Results

Of the 300 patients who were seen in the pain and palliative care clinic over the 16-month period of the chart review, 236 (79%) had advanced disease. The median age of the patients with advanced disease was 59 years (range, 21–87) and 43% were males. They had a heterogeneous representation with respect to their primary malignancy with more than 30 different primary cancer types being represented. However, lung, breast, and colorectal cancers were commonest, each comprising 10% to 15% of the sample (see Table 1).

In the advanced disease sample, 90% (212/236) of patients had a cancer other than breast cancer, and so were assigned one point for cancer type. Seventy-six percent (180/236) of patients had nonosseous metastases, and so were assigned one point for extent of disease. Only 27% (64/236) had a KPS $<70\%$, and were assigned one point for poor performance status. When the NRF scores were calculated, eight (3%) patients had an NRF score of 0, representing women with locally recurrent or bone-only metastatic breast cancer and a good performance status, usually on cancer treatment and often still going to work. Fifty-one (22%) had a score of 1, 125 (53%) had a score of 2, and 52 (22%) had a score of 3, typically a lung cancer patient with bone, liver, and brain metastases brought to the clinic in a wheelchair. Overall, 75% of the patient sample studied had a NRF score of 2 or 3.

As of April 30, 2012, 221 (94%) patients from the sample were recorded to have died, with an overall median survival of almost 5 months. Survival analysis (see Table 2) found that the NRF scores classifying the clinic population into four subgroups (NRF scores of 0, 1, 2, or 3) had median survivals of 15.4, 9.0, 4.6, and 2.1 months, respectively (Wilcoxon test $\chi^2=44.2$, degrees of freedom [*df*] 3, $p<0.0001$). The estimated 1-year survival of groups 0 to 3 was 62%, 39%, 21%, and 6%, respectively.

As the survival of the eight patients with a NRF score of 0 did not differ significantly from patients with a NRF score of 1, patients with NRF of 0 or 1 were combined into one group for the subsequent analyses. The Kaplan-Meier estimates of the survival curves for the three groups are shown by the solid lines (step-function) in Figure 1. The estimated 1-year mortality of the three groups was 58%, 79%, and 94%, respectively. The Wilcoxon test for the three groups was

$\chi^2=43.9$, *df* 2, $p<0.0001$. Pair-wise comparisons indicated highly significantly different survivals between groups ($p<0.001$).

The median, 25th percentile, and 75th percentile for survival (in months) for each of the subgroups 1, 2, and 3, is shown in Figure 2. These data reveal that the interval width becomes larger as the median survival increases, and there is overlap between the three subgroups. In other words, the prognostic groups are calibrated but they lack discriminative power at the individual level.

The survival curves in Figure 1 also show superimposed predicted survival based on a simple but accurate formula derived from fitting a log-logistic distribution to survival data from the three NRF groups [Probability (survive at least *M* months) = $A / (A + M^{1.4})$, where *A* = 27, 9, or 3, respectively, for NRF score = 0/1, 2, or 3]. Overlaying the simplified, rounded predictor with the Kaplan-Meier product-limit estimates, the curves are very close and the predictor remains well within the confidence limits of the Kaplan-Meier curves (not shown). Table 3 provides the probability (percentage chance) of being alive at various clinically relevant time points, for each of the NRF scores, according to the model.

Discussion

This is the first time that the NRF score has been subjected to validation beyond Canadian academic radiation oncology practice. In this case, it has been tested in a similar patient population but a different country and health care system from that in which it was developed, namely patients being seen for the first time by a palliative medicine physician in an outpatient clinic at an American comprehensive cancer center. The patients in this study had a variety of cancer types. Most were receiving some kind of antitumor treatment concurrently. In this setting, the NRF score was able to categorize patients into three distinct groups with different median survivals that were similar to those in the original study, with the typical patient from each of the three groups surviving around 3, 6, and 12 months, respectively. These median times points are likely to be important milestones for patients and families when making their plans, as well as for clinicians making treatment decisions, and for researchers stratifying patients for study design and analysis.

Although they were seen in a different setting, it was anticipated prior to undertaking the study that the patients in this sample would be similar to the patients seen by a radiation oncologist for palliation: almost all patients seen in the pain and palliative care clinic are referred for cancer pain management, so that the principal difference between radiation

TABLE 2. NUMERIC DETAILS OF KAPLAN-MEIER SURVIVAL CURVES, BY NRF SCORE SUBGROUPS

Score group	Number died	Number censored	Number patients	Median survival	95% confidence intervals for median survival	Lower quartile	Upper quartile
0	6	2	8	15.4	4.2, –	5.9	–
1	41	10	51	9.0	5.9–14.1	3.8	21.2
2	113	12	125	4.6	3.6–6.2	2.2	9.8
3	51	1	52	2.1	1.6–2.6	1.2	5.7
All 4	211	25	236	4.9	3.9–6.1	2.1	10.9

Median survival and quartiles are measured in months.
NFR, number of risk factors.

FIG. 1. Kaplan-Meier curve for NRF scores of 0 to 1, 2, and 3, with the predictive model overlying (broken lines).

oncology patients and these patients is the modality being offered to ameliorate their discomfort: analgesics versus radiation. Only a small minority was referred to this clinic for management of other symptoms or to discuss goals of care/hospice. Although the patient characteristics shown in Table

1 did reveal that pain and palliative care population was younger and more functional, with a greater heterogeneity of tumor type and less of a predominance of bone-only disease—the life tables for the palliative care patients were similar in exponential shape to those of the radiation oncology patients and the curves did not overlap, indicating that the model is robust and that there is a high level of calibration of the samples, and that the NRF score is transferable across populations and settings.

Whereas the NRF score appeared to be well calibrated at the group level, its predictive accuracy at the individual patient level was less clear (Fig. 2), on account of the wide range of observed survivals in each subgroup. There is overlap in the actual survivals of each subgroup, so that an individual patient with a NRF score of 3 may live longer than a patient with a NRF score of 1. In other words, the NRF score may not be an accurate predictor for individual patients, being unable to clearly discriminate between sicker patients and healthier ones. A larger sample size may lead to less overlap among NRF scores.

But even with a larger sample size and greater precision, variability in patient survival is always going to challenge the discriminative power of any prognostic tool at the individual patient level. Because the stereotypical question about life expectancy—“How long have I got?”—begs a simple, single-number answer such as “You have 6 months,”¹³ this sets up the belief, which may be unfounded, that a model for this purpose is waiting to be discovered, if only the right combination of factors can be found.

FIG. 2. Median and interquartile ranges for the three prognostic groups based on NRF scores, and the whole study population (“All”).

TABLE 3. PROBABILITY (PERCENTAGE CHANCE) OF BEING ALIVE AT VARIOUS CLINICALLY RELEVANT TIME POINTS, FOR EACH OF THE NRF SCORES

<i>NRF Score</i>	<i>1 month</i>	<i>2 months</i>	<i>3 months</i>	<i>6 months</i>	<i>9 months</i>	<i>1 year</i>	<i>18 months</i>	<i>2 years</i>	<i>5 years</i>
0-1	96	91	85	69	55	45	32	24	8
2	90	77	66	42	29	22	14	10	3
3	75	53	39	20	12	8	5	3	1

NRF, number of risk factors.

The prognostic information provided by the NRF can be utilized effectively at the individual level in two possible ways. The first approach is to combine the NRF group median with an appropriate communication strategy for discussing the prognosis with individual patients. A previous study of newly referred people with incurable cancer also showed that the survival curve is exponential and that the interquartile range and best and worst deciles for survival were wide but contained within simple multiples/fractions of the group median.¹⁴ Ranges and percentage probabilities were therefore proposed as more appropriately conveying the prognosis and its uncertainty than a single-point temporal estimate.¹⁴

The second approach is to use the prognostic model such as that developed from the NRF data and presented here to develop precise predictions of the patient's probability of being alive at any number of months, as shown in Table 3. As a worked example, a patient with a score of 0 to 1 has a median survival of 9 months, and the Kaplan-Meier estimate of the probability of being alive in 12 months is approximately 44.1%. The model $A/(A+M^{1.4})$ predicts a survival probability of 45.4%. To avoid the need for calculating fractional exponentials, $M^{1.4}$ may be approximated by a weighted average of M and $M^{1.5}$ ($M^{1.5} = M \times \text{square-root}(M)$), which can be readily performed on a pocket calculator with minor loss of predictive accuracy. For an NRF score of 0 to 1, this formula approximating $A/(A+M^{1.4})$ gives a probability of 1-year survival of 45.5%.

Although the NRF score may appear to be too simplistic to be useful, its components are known to be powerful predictive factors in cancer patients. Breast cancer has long been known to have a better outlook than other cancers, with a median survival measured in years, even without treatment.^{15,16} In breast cancer, patients with osseous metastases live substantially longer than those with visceral disease.¹⁷ Performance status is well known to be a strong prognostic factor in cancer patients.¹⁸ Although the KPS is subjective, it is physician-rated and has been used as the principal assessment tool for functional status in cancer patients for more than 60 years. Allocation of a KPS score <70 should be reliable, as it is distinguished by whether the patient is independent or not. Maintaining independence in one's activities of daily living is important in the ambulatory setting as disabled patients will have difficulty attending an outpatient clinic for treatment and follow-up.

Despite the fact these data appear to validate the NRF score, this study has definite limitations. It was tested in one practice at a comprehensive cancer center that focuses on one element of specialist palliative care and may not be applicable in other palliative medicine clinics. For example, the effect of treatment may impact on survival,¹⁹ and the use of chemotherapy may be different at a cancer center. This study

also had a relatively small sample size, and a larger sample size is likely to improve the precision of the median survival of each group and the discriminative power of the model, although there is always likely to be some overlap between group members at the individual level. The predictive power of the NRF score may be improved by the addition of other measures to the model, such as comorbidities and lab parameters. However, removal of symptom scores did not substantially impact on the development of NRF score,¹² and one of its most appealing features for the clinician is its parsimony.

A suite of prognostic calculators is available for ambulatory patients in geriatrics clinics,²⁰ and would be worth evaluating in palliative care outpatient clinics, especially in clinics with a large numbers of older patients with serious illnesses other than cancer. However, none of these tools is as easy to use in cancer patients as the NRF score, and in fact can be tedious to busy clinic physicians because of the amount of data that needs to be inputted to calculate the score. For example, one model requires 15 variables including patient demographics, a seven-item questionnaire on functional status and general health, number of medicines prescribed, and occurrence of previous hospitalizations to determine the 15-month all-cause mortality in community geriatric patients.²¹ Another prognostic index is capable of grouping patients according to the risk of dying in the next year after hospitalization into four distinct categories with similar mortalities to the four NRF model subgroups. It has a predictive accuracy of 75% to 80% and good discrimination and calibration.²² However, it requires six parameters to be inputted (gender, diagnosis, number of dependent activities of daily living at discharge, serum creatinine, and albumin) and has a complex scoring system (scores ranging from 0 to 26 with the four groups having scores of 0-1, 2-3, 4-6, and >6 points).

Conclusions

Predicting survival is important in palliative care for many reasons other than hospice eligibility. Distinguishing between ambulatory patients with weeks, months, or years to live is a technical prerequisite for excellence in clinical decision making and for research study design and analysis in addition to regulatory purposes. In ambulatory patients with advanced cancer, the NRF score shows promise as a clinically useful tool, especially when combined with an appropriate communication strategy for explaining the inherent prognostic uncertainty of living with advanced cancer. In addition, a model based on the NRF has been presented that enables the user to forecast precisely the probability of surviving any number of months for patients in each subgroup.

Further validation studies are needed in out-of-hospital palliative care programs before its widespread adoption can be recommended.

Author Disclosure Statement

No competing financial interests exist.

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