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Life expectancy in older adults with advanced cancer: Evaluation of a geriatric assessment-based prognostic model

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Abstract

Objectives—Oncologists estimate patients' prognosis to guide care. Evidence suggests oncologists tend to overestimate life expectancy, which can lead to care with questionable benefits. Information obtained from geriatric assessment may improve prognostication for older adults. In this study, we created a geriatric assessment-based prognostic model for older adults with advanced cancer and compared its performance to alternative models.

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Author contributions

The authors contributed to the following activities: (1) conceived of and designed analysis (JLL, PRD, SGM, LCH), (2) collected and managed data (SP, JKG, VGV, BLB, SGM), (3) contributed data or analysis tools (KPL, NG, SP, LL, APK, JKG, VGV, BLB, SGM, JYI), (4) performed or guided analysis (JLL, LL, AKP, JYI), and (5) wrote or critically revised paper (all authors).

Conflicts of Interest

Dr. Lund's spouse is a paid employee of GlaxoSmithKline and owns stock in the company. Dr. Loh reports being paid as a consultant to Pfizer and Seattle Genetics.

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All statements in this report, including its findings and conclusions, are solely those of the authors, do not necessarily represent the official views of the funding agencies, and do not necessarily represent the views of the Patient-Centered Outcomes Research Institute (PCORI), its Board of Governors, or Methodology Committee.

Materials and Methods: We conducted a secondary analysis of a trial (URCC 13070; PI: Mohile) capturing geriatric assessment and vital status up to one year for adults age ≥70 years with advanced cancer. Oncologists estimated life expectancy as 0-6 months, 7-12 months, and >1 year. Three statistical models were developed: (1) a model including age, sex, cancer type, and stage (basic model), (2) basic model + Karnofsky Performance Status (≤50, 60-70, and 80+) (KPS model), and (3) basic model + 16 binary indicators of geriatric assessment impairments (GA model). Cox regression was used to model one-year survival; c-indices and time-dependent c-statistics assessed model discrimination and stratified survival curves assessed model calibration.

Results: We included 484 participants; mean age was 75; 48% had gastrointestinal or lung cancer. Overall, 43% of patients died within one year. Oncologists classified prognosis accurately for 55% of patients, overestimated for 35%, and underestimated for 10%. C-indices were 0.61 (basic model), 0.62 (KPS model), and 0.63 (GA model). The GA model was well-calibrated.

Conclusions: The GA model showed moderate discrimination for survival, similar to alternative models, but calibration was improved. Further research is needed to optimize geriatric assessment-based prognostic models for use in older adults with advanced cancer.

Keywords

geriatric assessment; advanced cancer; prediction modeling

Introduction

Oncologists must use information available to them to estimate their patients' life expectancy to optimize decisions about cancer treatment and supportive care. Accurate estimation of life expectancy for older adults with cancer can be challenging due to heterogeneity in the presence of comorbidities, functional and cognitive impairments, and geriatric syndromes.[1–3] In the advanced cancer setting, several studies show that oncologists tend to overestimate their patients' life expectancy.[4–7] When oncologists overestimate life expectancy, they may miss opportunities to discuss transitions in goals of care and thus help patients prepare for end-of-life decisions.

As such, there is a need to improve oncologists' prediction of life expectancy among older adults with advanced cancers. One way to achieve this goal is by developing robust prognostic models that can (1) effectively distinguish between patients who are likely to die earlier versus later (i.e., discrimination) and (2) accurately capture observed survival across the range of predicted life expectancy estimates (i.e., calibration).[8] Researchers have attempted to use traditional oncology assessments like the Karnofsky Performance Status[9] (KPS) and Eastern Cooperative Oncology Group Performance Status for prognostication in patients with advanced cancer, but they have resulted in only moderate discrimination.[10] Other models have tried to incorporate symptoms[11,12] or intake and consciousness level,[11] but these efforts have resulted in little improvement in model discrimination. Thus, new approaches for improving prognostication among older adults with advanced cancers are needed.

Geriatric assessment,[13,14] a set of validated, patient-reported and objective measures to assess comorbidity, functional status, physical performance, cognitive status, psychological status, nutritional status, polypharmacy, and social support, has been shown to uncover age-related problems (e.g., cognitive impairment) not captured in standard oncology assessments.[15,16] Recent studies show that poor physical function and nutritional status captured via the geriatric assessment are associated with worse survival in older adults with advanced cancers.[17,18] While these studies highlight important prognostic factors in older adults with advanced cancers, they have not explicitly focused on evaluating the performance of prognostic models using the geriatric assessment. In this study, we create a geriatric assessment-based prognostic model and compare its performance (discrimination – overall and at specific time points - as well as calibration) to alternative models and oncologist-estimated life expectancy.

Materials and Methods

Data source and study population

We conducted a secondary analysis of a community-based, cluster-randomized trial.[19] The trial was conducted within the University of Rochester Cancer Center (URCC) National Cancer Institute Community Oncology Research Program (NCORP) and enrolled patients who were aged 70 years and above, had a diagnosis of an incurable stage III/IV solid tumor or lymphoma, had at least one (out of 8) impaired geriatric assessment domains other than polypharmacy, and were considering or receiving any kind of cancer treatment.[20,21] The treating oncologist was also enrolled. Individuals who had planned surgery or decided to forgo cancer treatment were excluded. For this study, participants who did not have a completed survival form (n= 57) were excluded, resulting in a study population of 484 patients and 121 oncologists. A comparison of patient characteristics from the included and excluded populations is provided in Supplemental Table 1.

Oncologist-reported measures

Two oncologist-reported measures were evaluated at study enrollment. The first was the treating oncologist's estimate of patient life expectancy assessed as follows: "Considering the patient's health, and underlying medical conditions, what would you estimate the patient's overall life expectancy to be?" This question was adapted from a previous study of seriously ill older patients (including those with cancer),[22] and this estimate was intended to include the current diagnosis of advanced cancer. Responses included 0-6 months, 7-12 months, 1 to 2 years, 2 to 5 years, >5 years. As active follow-up was only conducted for one year, we collapsed the responses for our analysis into the following categories: 0-6 months, 7-12 months, and >1 year.

The second measure was oncologist rated Karnofsky Performance Status (KPS),[9] reported only at patient enrollment as a range from 0% (dead) to 100% (normal, no evidence of disease). For analysis, we grouped KPS into three groups: 50% and lower, 60-70%, and 80% and higher.

Survival

Vital status and date of death or end of follow-up were ascertained using study forms and verified at each study site by the study coordinator. As part of the trial protocols, survival was assessed only up to one year following study enrollment.

Geriatric assessment

Geriatric assessment was performed at study enrollment, including 16 individual tests[19] covering the following health domains: physical performance, functional status, comorbidity, cognition, nutrition, social support, polypharmacy, and psychological health. For our analysis, we created a binary variable for each of these 16 tests to indicate whether a deficit was present or not, as done previously in the COACH trial (see detailed content published elsewhere[20,21]).

Other patient characteristics

The trial also recorded demographic information including self-reported age, gender, and race/ethnicity. Cancer type and stage were assessed at enrollment. Additional self-reported information regarding marital status, household income, and educational attainment were also collected at enrollment.

Statistical analysis

Characteristics of the study population were summarized. Kaplan-Meier methods were used to describe survival at one year. Among those with complete data (n=429), we compared the oncologists' estimates with observed survival and measured agreement based on the three categories (0-6 months, 7-12 months, and >1 year) using the weighted kappa.[23]

We constructed three statistical models to predict survival. The basic model included age, sex, cancer type, and stage, representing information routinely available to oncologists. The KPS model included the basic model plus the addition of KPS categories (50% and lower, 60-70%, and 80% and higher), allowing exploration of whether and how subjective KPS assessment improves prognostication. Third, the GA model included the basic model plus the 16 binary indicators of geriatric assessment-defined deficits. We did not include KPS in the GA model as we wanted to describe the performance of a model that used objective measures of geriatric health instead of subjective assessments for prognostication. Finally, we also evaluated the performance of oncologists' life expectancy estimates in predicting survival, which likely includes both objective assessment of the health status and tumor characteristics, but also subjective assessments that may reflect the oncologists' clinical impression of fitness or frailty. However, we do not refer to this as a model, as it only represents a single variable.

Cox proportional hazards regression was used to model one-year survival as a function of the specified model predictors. Model discrimination measures the predictive ability of a model to accurately rank individuals according to their survival time. We evaluated model discrimination via ten-fold cross-validation[24] using Harrell's concordance statistic (or c-index),[25] as well as the time-dependent area under the receiver operating curve (AUC) or c-statistic evaluated at 30, 90, 180, and 365 days. Concordance statistics range from

0 to 1 with a value of 0.5 representing prediction no better than chance. Concordance statistics ranging from 0.5-0.6 are often considered as poor, 0.6-0.7 as moderate, 0.7-0.8 as good, 0.8-0.9 as very good, and 0.9 and above as excellent.[26] Calibration, or the agreement between the model-predicted and observed survival estimates,[27] was visually inspected. We plotted stratified observed versus model-predicted survival curves by approximating the baseline survival function within four prognostic groups, defined at the 18th, 50th, and 84th percentiles, using methods described by Royston et al.[28] Observed and model-predicted curves that largely overlap suggest well-calibrated models. As the oncologist model was a simple stratification of observed survival across three prognostic groups, we plotted observed survival only.

The University of North Carolina at Chapel Hill Institutional Review Board (IRB) determined this research to be exempt from IRB review.

Results

Patient characteristics and overall survival

Table 1 summarizes the characteristics of the study population. In total, 484 patients were included in the study with a median age of 75 years and almost half were diagnosed with a gastrointestinal or lung cancer. The median time from advanced cancer diagnosis to study enrollment was 227 days. Among the 16 individual geriatric assessment tests, the most common deficit identified was polypharmacy (84%) followed by deficits in physical performance defined by the Short Physical Performance Battery (81%) and the OARS Physical Health (75%).

Overall, 43% of the population died within one year. Among patients with known survival times and oncologist generated life expectancy estimates (n=429, Table 2), oncologists estimated that 23 patients (5%) would survive 0-6 months, 93 patients (22%) would survive 7-12 months, and 313 patients (73%) would survive >1 year. This is contrasted with actual survival where 105 patients (24%) died within 0-6 months, 84 patients (20%) died within 7-12 months, and only 240 patients (56%) survived to >1 year. Overall, oncologists' accurately estimated life expectancy in 55% of patients, but overestimated life expectancy in 35% of patients and underestimated it in 10% of patients (weighted kappa=0.21).

Prognostic model performance

Discrimination—Table 3 reports Harrell's c-index indicating the discrimination between predicted and observed survival times based on each model, as well as the c-statistic at each specific time point. Overall, the GA model resulted in the highest c-index of 0.63 (0.56, 0.69), but was similar to the c-indices for the basic model of 0.61 (0.59, 0.65), the KPS model of 0.62 (0.55, 0.68), and oncologists' life expectancy estimates of 0.61 (0.50, 0.71). The time-dependent c-statistic for the KPS model and oncologists' life expectancy estimates were highest for the 30-day time point and decreased slightly over time, whereas the time-dependent c-statistic was relatively stable across time for the basic and GA models. Parameter estimates from all models are included in Supplemental Tables 2–5.

Calibration—Figure 1A–C shows the predicted and observed survival curves for the four statistical models stratified by four prognostic groups identified by the 18th, 50th, and 84th percentiles of survival times. The dashed lines represent the predicted survival times and the solid lines represent the observed survival times. Figure 1D displays observed survival across the three oncologist-estimated life expectancy categories. The basic model showed good calibration with observed and predicted curves largely overlapping, with slight underestimation of survival in the highest quartile group. The KPS model had the worst calibration, with underestimation of survival in the lowest survival quartile but overestimation in the second to lowest survival quartile. Finally, the GA model was generally well-calibrated with curves overlapping, with slight overestimation of survival in the highest quartile group. In general, the spread between the four lines was most pronounced in the GA model, with improved distinction of the lowest survival group.

Discussion

In this study enrolling older adults with advanced cancer, we found that prognostic models using commonly available clinical information or augmented by additional data from GA had moderate discrimination of survival. Discrimination using these models was similar to oncologists' life expectancy estimates alone. However, our results suggest that information from GA can enhance model calibration, an important but often overlooked aspect of predictive performance.[29] Poorly calibrated models that, for example, overestimate life expectancy can lead to overly aggressive treatment decisions and delayed referrals to palliative care or hospice, while model that underestimate life expectancy may lead to withholding potentially beneficial therapy.

We also reported variation in discriminative performance of the four models over time. Interestingly, the time-dependent c-statistic at 30-days for the oncologists' life expectancy estimates and KPS model were 0.77 and 0.73, respectively, while only 0.61 for the basic and 0.65 for the GA models. Despite the imprecision of these estimates due the occurrence of few early events, this finding may reflect oncologists' ability to subjectively perceive when a patient is imminently dying, which other objective tools cannot detect. Taken together, our evaluation of time-dependent discrimination suggests that the selection of a specific prognostic model to inform decision-making will depend, to some extent, on the relevant time horizon for the decision.

Prognostic models of life expectancy in general populations of older adults, such as the Schonberg, Lee, and Lund-Lewis models, have reported c-statistics or c-indices in the range of 0.75-0.83.[30–34] These models incorporate similar domains of health as the geriatric assessment, including comorbidities and activities of daily living. So, why are these models so much more successful in discriminating survival than the models evaluated in our study? In a general pool of older adults, there is greater variation in health status and prognosis than in a restricted cohort of older adults with advanced cancer, where prognosis is generally poor overall. This restriction in prognostic profiles makes it more challenging to separate those who are likely to die early from those who are likely to die later.
So, how can we surmount this challenge and improve discriminative performance? One potential approach for future work is to incorporate more diverse sources of information

for determining prognosis by including subjective assessments from patients, caregivers, and oncologists alongside objective assessments of cancer features and measures of geriatric health. A recent study of older adults with prostate cancer suggests that adding patient-reported outcomes to other claims-based indicators of health may improve prognostic discrimination.[35] Another approach would be to utilize the full-extent of detail contained within the geriatric assessment for model prediction. Our current analysis included only binary indicators of geriatric assessment results using pre-selected cutpoints,[19] which results in the loss of predictive information. Instead of using cut-points, future research should examine use of the entire range of assessment scores for prognostication. Finally, instead of focusing on improving discriminative model performance, prognostic tools could instead focus on embracing some uncertainty and transparently communicating that uncertainty to patients. There is ongoing research investigating the use of best case, worst case, and typical scenarios in prognostic communication to patients with advanced cancer,[36–38] indicating this is largely an acceptable communication strategy.

Results from this study should be viewed considering several points. First, vital status was assessed through active follow-up; therefore, survival times were unknown for those without a returned form. However, characteristics of patients missing a survival time were similar to those with an observed survival time, and thus selection bias is unlikely. Second, in the trial, oncologists' life expectancy estimates were categorized into windows of time (i.e., 0-6 months, 7-12 months, >1 year), which leads to a loss of information. In turn, this categorization can incorrectly classify an oncologist's estimate as inaccurate even when it is largely accurate (e.g., an oncologist's estimates life expectancy at 7 months – categorized as 7-12 months – but the patient dies in month 6 (categorized as 0-6 months observed survival). Because of this categorization of oncologists' life expectancy estimates in this secondary analysis of trial data, we could not directly compare our findings with previous studies that reported oncologist-estimated life expectancy by weeks or months.[37] Third, we did not have access to information on cancer treatment history or specific tumor markers, which could potentially improve survival prediction. Ultimately, for this information to be useful for real-time clinical prognostication, it has to be collected in a consistent, standardized, and structured format in all patient records. Fourth, we internally validated our models using established cross-validation methods;[24] however, external validation is a critical step for establishing the value of all prognostic models.[39] Finally, recent trials[19,40–44] have demonstrated clear benefits of geriatric assessment as a supportive care intervention for older adults with advanced cancers to identify vulnerabilities, reduce chemotherapy toxicity, improve communication, satisfaction with care, and quality of life. Therefore, regardless of the findings of the present study, geriatric assessment is a useful tool for improving patient-centered outcomes and is now recommended by the American Society for Clinical Oncology.[1,2]

In summary, we found that a prognostic model combining common clinical data with geriatric assessment showed moderate discrimination of one-year survival and improved calibration over other approaches to prognostic estimation. Accurate prognostication in this population is critical, as it plays a central role in individualized treatment decision-making. Efforts to further improve prognostic model performance through integration of

information from patients, caregivers, and oncologists and more flexible analytic approaches are warranted.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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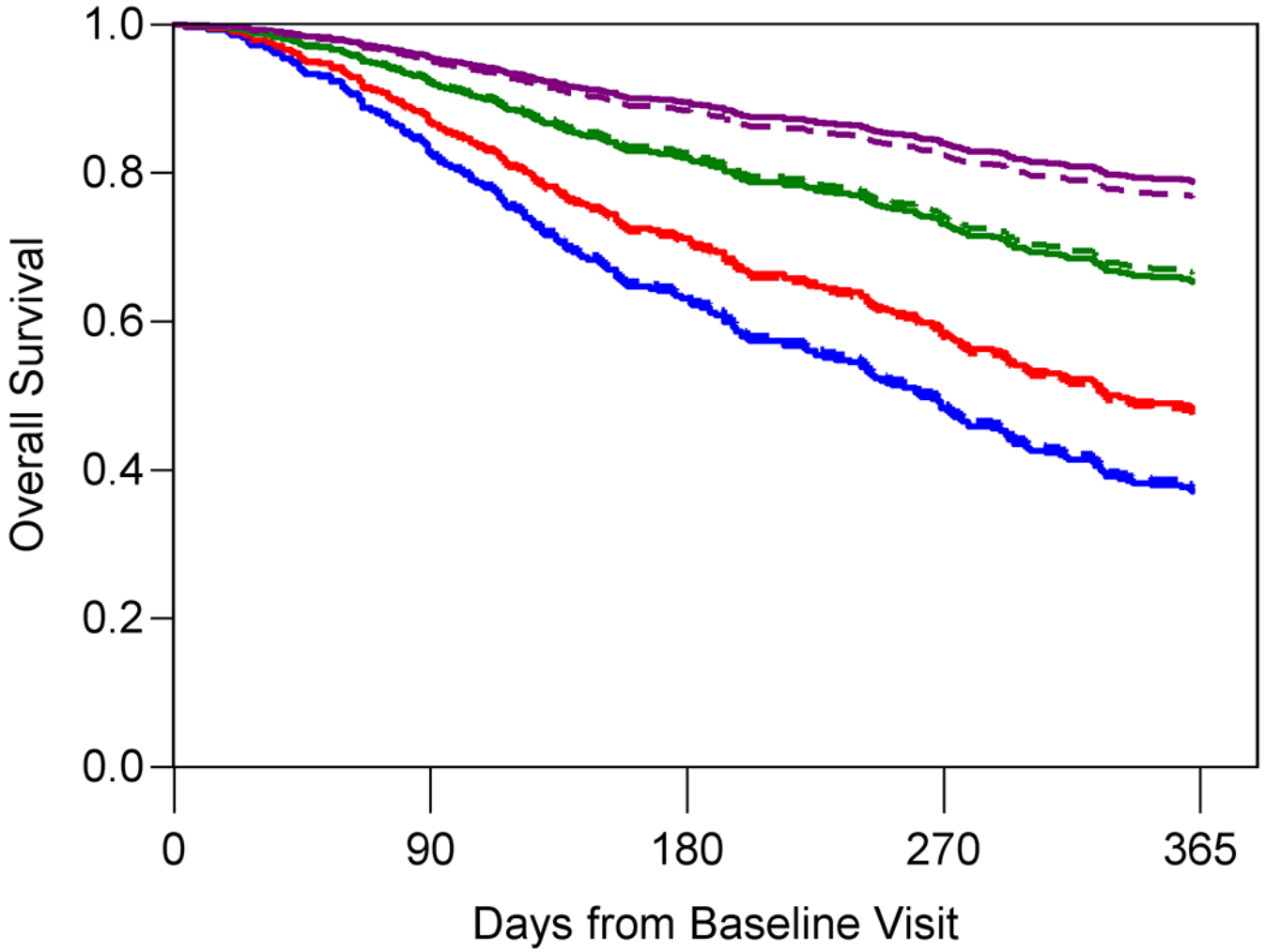

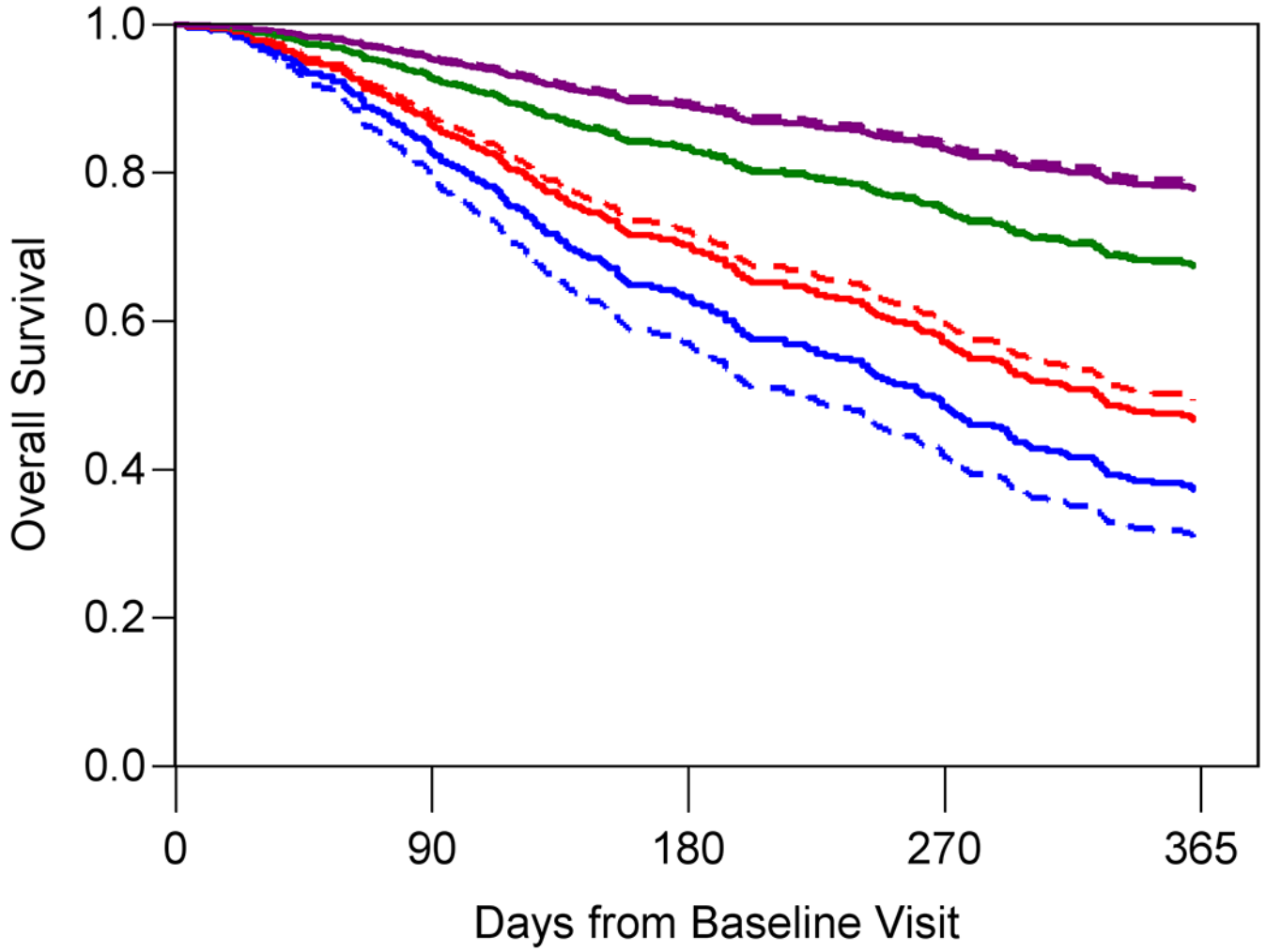

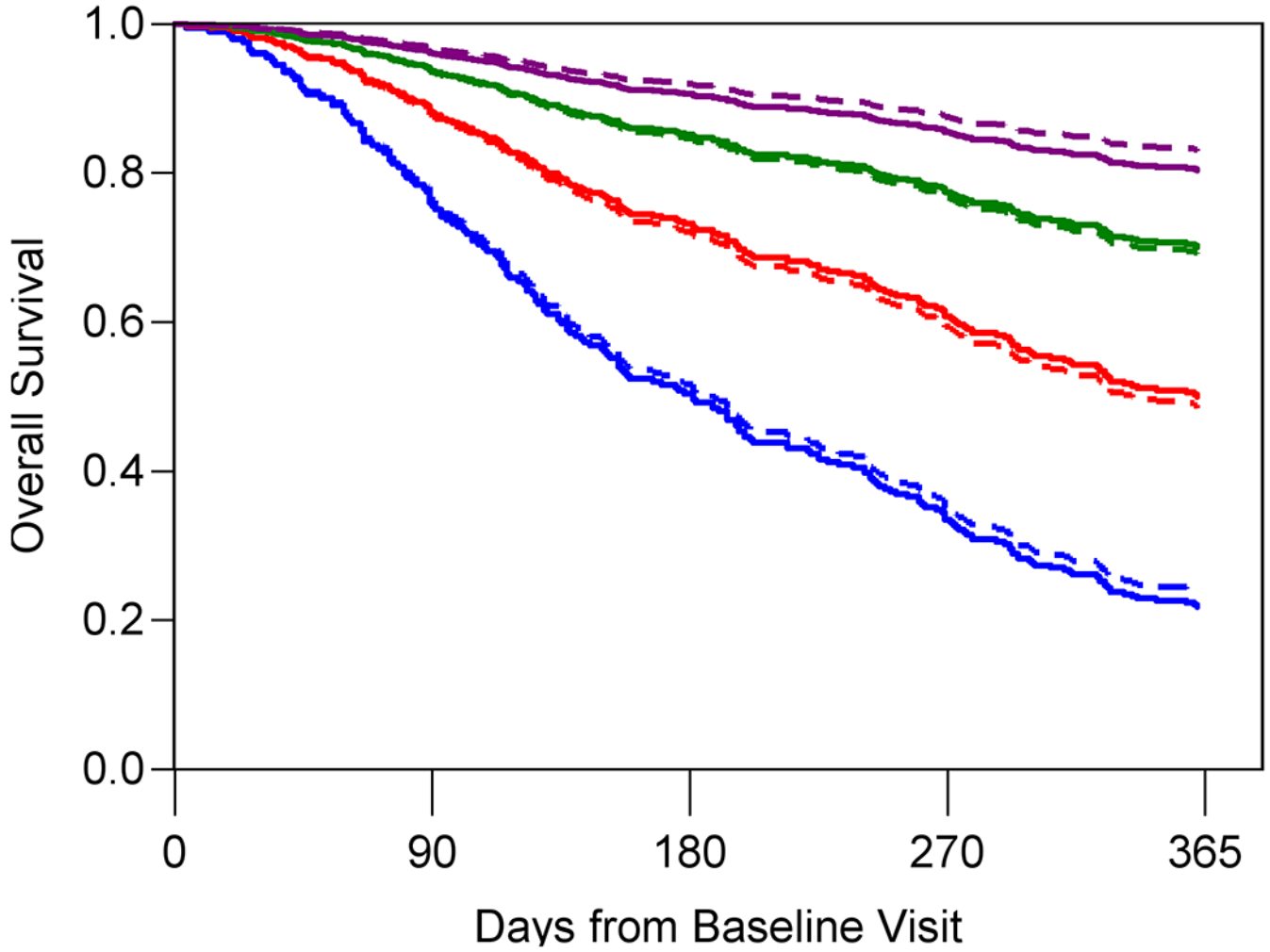

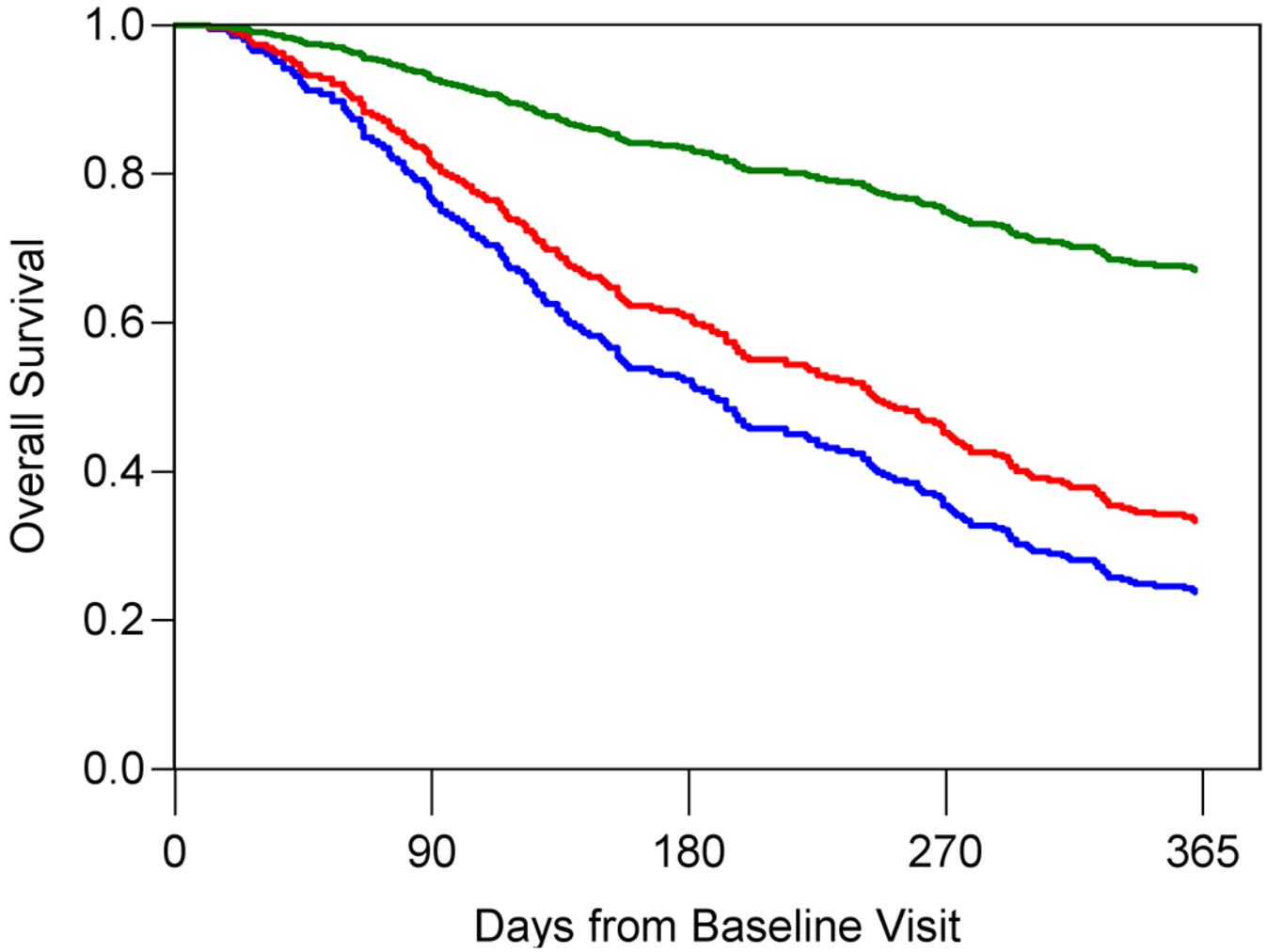

Figure 1A-D. Stratified survival curves to assess calibration for three prediction models and oncologists' prognostic estimates.

The blue, red, green, and purple lines represent the model-predicted survival times for patients in the <18th percentile, between the 18th and <50th percentile, between the 50th and <84th percentile and >84th percentile, respectively. The dashed lines represent the predicted survival times and the solid lines represent the observed survival times. Panel D only include three observed lines as the Oncologist model is a simple stratification of observed survival based on three prognostic categories: 0-6 months (blue), 7-12 months (red), and 1+ year (green). Observed and model-predicted curves that largely overlap suggest well-calibrated models.

Table 1.

Characteristics of 484 Participants Included in the Study Population

Patient characteristics*	n	%
Age, median years (IQR)	75 (72, 80)	
Sex		
Female	238	49
Male	245	51
Time from advanced cancer diagnosis to enrollment, median days (IQR)	227 (65, 660)	
Cancer type		
Gastrointestinal	116	24
Lung	117	24
Breast	66	14
Genitourinary	67	14
Other	117	24
Stage		
III	43	9
IV	427	88
Other	13	3
Domain: Polypharmacy		
Polypharmacy (5+ medications)	408	84
Domain: Cognition		
BLESSED Orientation-Memory-Concentration	11	2
Mini Cog (based on word recall and clock drawing)	166	34
Domain: Nutrition		
Weight loss (>10% change from 6 months ago)	71	15
Body mass index <21 (low weight)	60	12
Mini Nutrition Assessment (≤ 11 points)	278	57
Domain: Physical Performance		
Timed “Up and Go” (≥ 13.5 seconds)	200	41
Short Physical Performance Battery (≤ 9 points)	392	81
Falls (any history of falls in the prior 6 months)	125	26
OARS Physical Health (any limitation defined as “a lot”)	364	75
Domain: Functional Status		
Activities of Daily Living (any deficit identified)	138	29
Instrumental Activities of Daily Living (requiring help or unable to do)	275	57
Domain: Comorbidity		
OARS Comorbidity (3 illnesses or 1 that interferes a great deal)	308	64
Domain: Psychological Health		
Generalized Anxiety Disorder-7 (≥ 10 points)	39	8
Geriatric Depression Scale (≥ 5 points)	106	22
Domain: Social Support		
OARS Medical Social Support (as “some”, “a little”, or “none of the time”)	143	30

Patient characteristics*	**n**	**%**
Estimated life expectancy		
0-6 months	29	6
7-12 months	106	22
1+years	340	70
Missing	9	2

* A description for each assessment tool and associated cut-points can be found in references 18 and 19.

Table 2.

Cross-Classification of Oncologist-Estimated Life Expectancy and Observed Survival in the Trial Participants with Complete Data.

	Actual survival			
Oncologist estimate	**0-6 months**	**7-12 months**	**1+ years**	**Total**
0-6 months	10 (2.3%)	8 (1.9%)	5 (1.2%)	23 (5.4%)
7-12 months	43 (10.0%)	20 (4.7%)	30 (7.0%)	93 (21.7%)
1+ years	52 (12.1%)	56 (13.1%)	205 (47.8%)	313 (73.0%)
Total	105 (24.5%)	84 (19.6%)	240 (55.9%)	429 (100%)

Note: The analysis is limited to patients with complete information on oncologist-estimated life expectancy and non-censored survival times (i.e., complete follow-up through one year from enrollment). The classification table displays agreement and disagreement between oncologists' estimates of life expectancy (rows) and observed survival (columns). Oncologists' overestimation of survival is noted in light grey, while underestimation is noted in dark grey. All percentages represent cell percentages (i.e., a proportion of the total number of study participants with complete information, n=429).

Table 3.

C-Indices and Time-Dependent Areas Under the Receiver Operating Curves for the Three Multivariable Models and for Oncologist-Reported Life Expectancy Estimates

	Basic model	KPS model	GA model	
Measure	**Age, sex, cancer type, and stage**	**Basic model + KPS**	**Basic model + 16 GA impairments**	**Oncologist-estimated life expectancy categories**
C-index (95% CI)	0.59 (0.54, 0.65)	0.62 (0.55, 0.68)	0.63 (0.56, 0.69)	0.61 (0.5, 0.71)
Time-dependent AUC (95% CI)				
30 days	0.61 (0.21, 1.00)	0.73 (0.44, 1.00)	0.65 (0.39, 0.91)	0.77 (0.33, 1.00)
90 days	0.62 (0.54, 0.70)	0.67 (0.54, 0.80)	0.68 (0.57, 0.79)	0.67 (0.48, 0.87)
180 days	0.61 (0.53, 0.69)	0.64 (0.55, 0.73)	0.66 (0.60, 0.72)	0.65 (0.45, 0.84)
365 days	0.61 (0.52, 0.69)	0.63 (0.54, 0.73)	0.65 (0.56, 0.74)	0.64 (0.51, 0.76)

*Abbreviations: area under the receiver operating curve=AUC, Karnofsky Performance Status=KPS, geriatric assessment=GA, confidence interval=CI