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Development of Imminent Mortality Predictor for Advanced Cancer (IMPAC), a Tool to Predict Short-Term Mortality in Hospitalized Patients With Advanced Cancer

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QUESTION ASKED: End-of-life care for patients with advanced cancer is aggressive and costly. Oncologists inconsistently estimate life expectancy and address goals of care. Current available prognostication tools are based on subjective clinical assessment. We asked whether we could use objective data from the Electronic Health Record to develop the Imminent Mortality Predictor in Advanced Cancer (IMPAC), a tool that could predict short-term mortality in hospitalized patients with advanced cancer. If so, such a tool could be used by oncologists to guide end-of-life conversations.

SUMMARY ANSWER: For mortality within 90 days at a 40% sensitivity level, IMPAC has close to 60% positive predictive value. Patients estimated to have a greater than 50% chance of death within 90 days had a median survival time of 47 days. Patients estimated to have a less than 50% chance of death had a median survival of 290 days (Fig).

METHODS: Statistical learning techniques were applied to data from electronic health records (EHRs) for 669 patients with advanced cancer discharged from Yale Cancer Center/Smilow Cancer Hospital to develop a tool that could estimate survival probabilities. To characterize the pattern of end-of-life care among this cohort, we examined the use of aggressive interventions within the last 30 days of life. For every visit in which IMPAC correctly identified the patient as likely to die within 90 days of admission, we calculated the potentially avoidable cost had the patient instead been cared for in hospice.

BIAS, CONFOUNDING FACTOR(S), DRAWBACKS: The data used to generate the model were based on patterns of care at a single academic research institution in which patients and physicians could self-select for more aggressive care. IMPAC uses data from the Rothman Index, a proprietary commercial product, thus limiting applicability at hospitals that do not purchase it. Our cost avoidance model is built on the assumption that patients flagged as likely to die would all receive only hospice care from 48 hours into a hospitalization onward and does not incorporate actual cost data from patients transitioned to hospice.

REAL-LIFE IMPLICATIONS: We have developed a novel prognostic tool, IMPAC, which uses objective data to generate life expectancy probabilities automatically from EHR data in real time. If it is integrated into the standard clinical workflow, IMPAC will signal oncologists that goals-of-care conversations are imperative and will help facilitate prognostic understanding and informed decisions regarding downstream health care interventions. Potentially avoidable costs are significant. JOP

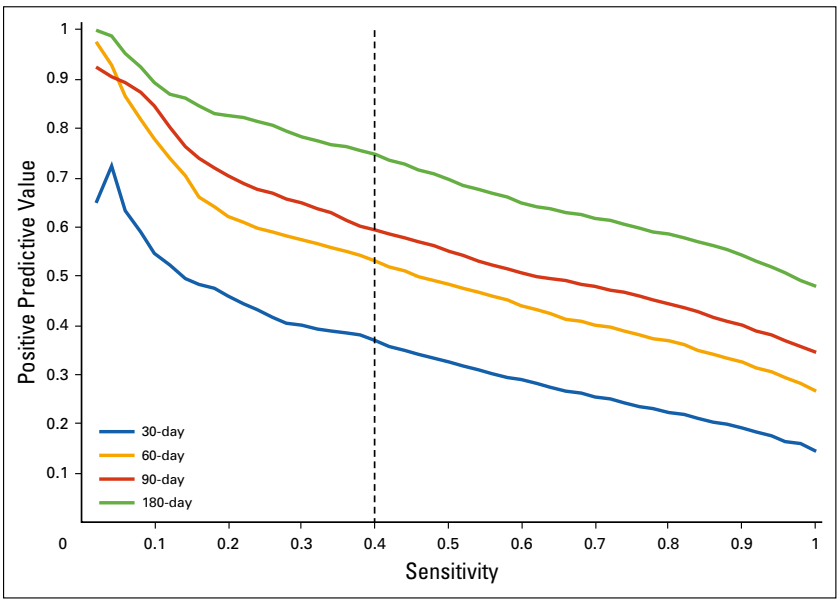

Fig. Average positive predictive value versus sensitivity for 30-, 60-, 90-, and 180-day mortality horizons. The average value is taken across the 20 test set splits.

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Abstract

Purpose

End-of-life care for patients with advanced cancer is aggressive and costly. Oncologists inconsistently estimate life expectancy and address goals of care. Currently available prognostication tools are based on subjective clinical assessment. An objective prognostic tool could help oncologists and patients decide on a realistic plan for end-of-life care. We developed a predictive model (Imminent Mortality Predictor in Advanced Cancer [IMPAC]) for short-term mortality in hospitalized patients with advanced cancer.

Methods

Electronic health record data from 669 patients with advanced cancer who were discharged from Yale Cancer Center/Smilow Cancer Hospital were extracted. Statistical learning techniques were used to develop a tool to estimate survival probabilities. Patients were randomly split into training (70%) and validation (30%) sets 20 times. We tested the predictive properties of IMPAC for mortality at 30, 60, 90, and 180 days past the day of admission.

Results

For mortality within 90 days at a 40% sensitivity level, IMPAC has close to 60% positive predictive value. Patients estimated to have a greater than 50% chance of death within 90 days had a median survival time of 47 days. Patients estimated to have a less than 50% chance of death had a median survival of 290 days. Area under the receiver operating characteristic curve for IMPAC averaged greater than .70 for all time horizons tested. Estimated potential cost savings per patient was $15,413 (95% CI, $9,162 to $21,665) in 2014 constant dollars.

Conclusion

IMPAC, a novel prognostic tool, can generate life expectancy probabilities in real time and support oncologists in counseling patients about end-of-life care. Potentially avoidable costs are significant.

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INTRODUCTION

End-of-life care for patients with advanced cancer is aggressive, costly, and often discordant with patients' wishes.[1-4] Among Medicare decedents, 80% were hospitalized within 90 days of death, 27% were admitted to the intensive care unit (ICU) within 30 days, and 20% transitioned to hospice in the last 3 days.[5] Thirty percent of all spending for cancer occurs in the last year of life.[6,7]

Patients with advanced cancer rely on their oncologists to guide end-of-life care decisions. However, oncologists' estimation of life expectancy is often inaccurate[8,9] and overly optimistic.[10,11] Current prognostication tools are limited by dependence on subjective assessment.[8] Instruments have been developed to stratify the risk of dying in the near term,[12-14] but most, like the Palliative Prognostic Index,[12] use subjective physician assessments, static data, and statistical techniques that do not make full use of data available in electronic health record (EHR) systems. Estimation of life expectancy could be improved by objective and reproducible prognostic tools.[15,16]

In this article, we explain the development of a new prognostic tool, the Imminent Mortality Predictor in Advanced Cancer (IMPAC), which uses objective clinical data to predict when a patient has a limited life expectancy. Ultimately, if such a tool were embedded in the EHR and incorporated into standard clinical workflow, it could indicate when end-of-life conversations are imperative, improve patients' and oncologists' prognostic awareness, and facilitate shared decision making about future interventions.

IMPAC is designed to assess mortality risk for patients with advanced cancer who undergo at least one hospitalization, and it has several novel features. It uses objective data drawn from the EHR and incorporates both static and time series data. IMPAC uses statistical learning techniques to identify geometric features of the time series data that are useful in prognosis. The tool can be integrated into EHR systems and can automatically generate a probability of mortality at 30, 60, 90, and 180 days from the time of admission. We also calculate the cost of care for a subset of the patients correctly identified by IMPAC and estimate the potential cost avoidance if they had been cared for in an alternative environment (hospice).

METHODS

Study Population

We examined the inpatient records of 773 unique patients with advanced solid tumors identified by the Yale New Haven Hospital tumor registry with a hospital discharge (for any cause of admission) between October 1, 2013, and September 31, 2014.

Data Collection and Measurements

We used a metric available in the EHR at Yale New Haven Hospital, the Rothman Index (RI; PeraHealth).[17] RI is a real-time, EHR-based scalar measure of patient acuity that is continually calculated throughout the hospitalization and has been incorporated into most commercially available EHRs.[17,18] It incorporates 26 clinical data elements, including vital signs, nursing assessments, and laboratory results, and has been shown in multiple settings to predict both mortality[17,19] and readmission.[17-21] In patients who have cancer, lower RI scores predict the likelihood of inpatient death or discharge to hospice as well as hospital readmission.[22]

To ensure that enough RI scores were spread across a sufficient period to inform the model, we excluded visits with less than 48 hours of RI monitoring (excluding 71 patients) and for which no RI was available between 36 and 48 hours (33 excluded). The final data set consisted of 669 unique patients with 1,073 inpatient encounters. Because IMPAC is intended for visits that meet these criteria, the exclusions should not bias the predictions for the target population.

In addition to the RI time series for each patient encounter, the initial model included 22 static variables derived from the patient- and visit-level variables listed in Table 1; some were removed during the variable selection process described in the Statistical Methods section to arrive at the final model. Patients' survival status was collected from the institutional tumor registry as of September 9, 2017. For patients with more than one hospitalization during the study period, each visit was treated as a separate observation.

Statistical Methods

We used functional principal components analysis[23] to transform each patient encounter RI trajectory into a set of weights. Functional principal components analysis is a statistical algorithm that identifies a small set of curves that when appropriately weighted and summed can closely represent the RI trajectories. In other words, if $RI_k(t)$ is the RI trajectory for the k-th encounter (as a function of time t), then

$$RI_k(t) = w_{k,1} \times pc_1(t) + w_{k,2} \times pc_2(t) + \ldots + w_{k,m} \times pc_m(t),$$

where $pc\_1(t),\ldots,pc\_m(t)$ are the principal curves, and $w_{k,1},\ldots,w_{k,m}$ are the associated weights for the k-th encounter. The set

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Table 1. Patient Characteristic Summary Data

Characteristic	No.	%	Quartile
Patient specific	669		
Mean age, years (SD)*	63 (12)		
Males		46.0	
Visit specific	1,073		
Entry through emergency department*		41.0	
Prior visit in the last 90 days*		35.0	
Length of stay, days			3, 5, 9
Time to event, days			
Censoring		38.2	22, 59, 161
Death		61.8	26, 59, 184
Type of cancer			
Breast		7.3	
Endocrine		2.4	
GI		24.0	
Genitourinary		5.8	
Gynecologic		15.0	
Head and neck*		10.0	
Melanoma		3.5	
Neurologic*		7.9	
Sarcoma		4.9	
Thoracic		18.0	
Undefined and unknown		0.74	

Abbreviation: SD, standard deviation.
*Variables selected under the Akaike information criterion for use in the prognostic model.

of curves is common to all encounters, and the weights measure how closely the trajectory resembles each curve. We used the visit-specific weights and 22 static variables as predictors of mortality. If the regression coefficient for a particular weight is positive and significant, then trajectories that resemble the shape of the corresponding curve are associated with higher mortality.

We randomly split the patients into training and validation sets so that approximately 70% of visits were in the training set and 30% were in the validation set. We ran the algorithm with 20 different random splits of total visits. With 20 random samples, the chance of an individual patient not appearing in any of the validation sets was only .0008. We confirmed that each patient appeared in at least one validation set. We applied the Cox proportional hazards model to the training set to estimate the mortality hazard function from which survival probability predictions could be estimated. We used the Akaike information criterion (AIC)[24] to remove variables with insignificant predictive power from the final model. AIC is a standard variable selection technique that penalizes complicated models (many variables) that offer little improvement over simpler ones, thus guarding against overfitting.

For patients with multiple observations, the start of the first observation was the time of first admission within the study period, and the end was the time of the next admission. The observation is considered right-censored if the patient is still alive at the end of the period. Subsequent observations were defined in the same manner except if the last one was followed by death, in which case the observation ended on the death date. Patients still alive on March 31, 2015 were considered right-censored.

To assess model accuracy, we used several approaches. First, we applied each of the 20 fitted models prospectively to their corresponding test set, yielding an estimate of the probability of death within N days for each visit (for $N = 30, 60, 90, 180$). If the probability exceeded a prespecified threshold t% (eg, 50%), it was classified as likely to be followed by death within N days. We compared the classification against the actual outcome and calculated sensitivity and positive predictive value (PPV). For this model, sensitivity demonstrates the model's ability to identify patients who ultimately die within the defined time period, whereas PPV measures accuracy (ie, whether a patient predicted to die actually does). Second, we used Kaplan-Meier curves to estimate and compare survival times for true positives, false positives, true negatives, and false negatives. Third, we generated standard receiver operating characteristic curves. All computations were performed by using R software.

Determination of Potential Avoidable Care

For every visit in which IMPAC correctly identified the patient as likely to die within 90 days of admission, we calculated the potentially avoidable cost using Yale New Haven Health System's cost accounting system. We classified all procedures and interventions between IMPAC's prediction and the time of actual death as potentially avoidable. We extracted direct cost data for products and services incurred at the hospital after the 48-hour patient assessment period of the index admission and during all subsequent inpatient and outpatient visits. Direct costs are patient care related (eg, radiology, nursing, laboratory). Hospital indirect costs, physician services, and costs incurred outside of our health system were excluded.

The potentially avoidable costs were then compared with costs associated with hospice care for the same duration, based on the assumption that IMPAC would divert patients who are predicted to die soon into hospice care and thus avoid unnecessary interventions. We assume that these patients receive

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hospice care for the remainder of their lives and that survival time under hospice care is the same as in an acute care facility.

Hospice costs were calculated on the basis of 2014 national hospice data[25] showing the daily payment for four levels of care: routine home care, 93.8% at $156; general inpatient care, 4.8% at $694; continuous care, 1.0% at $91; and respite care, 0.4% at $161 daily rate. These were used to approximate an average daily hospice cost which, when multiplied by the total inpatient length of stay after IMPAC's prediction of death, approximated the cost of hospice care used for comparison.

RESULTS

Prognostic Tool

We identified 13 principal component curves that captured the variability of the RI trajectories. Of the principal component weights, only the first one was selected by AIC to predict mortality, and its regression coefficient was negative. Hence, trajectories with a large negative weight on the first principal curve (Fig 1) are at an elevated risk of death. Such trajectories resemble the inverted shape of the curve in Figure 1. In addition, patient age, entry through the emergency department, prior hospitalization within 90 days, and diagnosis of head and neck or neurologic cancer were also selected by AIC. This final set of predictors was consistently selected across 20 different random splits of the data into training and test sets and across survival durations.

Figure 2 shows the average PPV for each sensitivity level. For example, for mortality within 90 days at a 40% sensitivity level, IMPAC has a 60% PPV. In other words, using a probability threshold for classifying a visit as likely to result in death within 90 days such that we capture 40% of the visits for which that happens, we are correct 60% of the time.

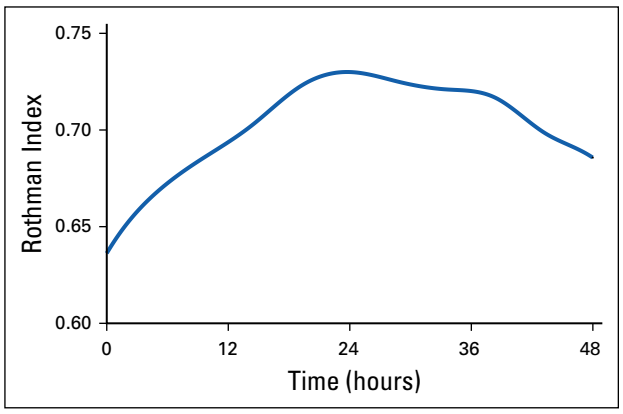

Fig 1. Scaled shape of the first principal component curve.

Another way to assess the accuracy of IMPAC is to examine the survival distribution for the false positives. We focus on 90-day predictions using a 50% probability of death as a classification threshold (Fig 3). The median patient incorrectly predicted to die within 90 days lived an extra 4 months (median survival of 229 days), whereas the true-negative patients lived a median of 526 days. Combining all patients estimated to have at least a 50% chance of dying within 90 days yields a median survival time of 47 days. Those estimated to have a less than 50% chance of dying within 90 days had median survival time of 290 days. These survival time statistics indicate that IMPAC identifies patients who are likely to die significantly sooner than others, if not exactly within 90 days.

We also generated the traditional receiver operating characteristic curves for the four life expectancy predictions averaged across 20 partitions of the sample. The areas under the curves are .736, .722, .710, and .717 for the 30-, 60-, 90-, and 180-day predictions, respectively.

End-of-Life Care

We analyzed the use of aggressive interventions within 30 days of death among patients with advanced solid tumors who had an inpatient admission from October 2013 to September 2014. In the study population, 27% of patients were admitted to the ICU (average, 2.2 times), 38% visited the emergency department (average, 2.3 times), 52% were admitted to acute care inpatient service (average, 2.1 times), 18% received chemotherapy, 13% received nonpalliative radiation, and 3% underwent a major surgical procedure. Of 1,073 inpatient encounters, 404 were followed by another hospitalization and 425 resulted in subsequent death: 150 (14%), 278 (26%), 370 (34%), and 540 (47%) died within 30, 60, 90, and 180 days of admission, respectively.

Cost Avoidance

To estimate the potentially avoidable cost of treatment, we selected one specific test set with the probability of death within 90 days threshold set at 50% and did a closer analysis of those patients. For this set of 309 inpatient encounters, 103 resulted in death within 90 days, and IMPAC correctly identified 41 of those encounters (38 unique patients). For the 41 encounters, the first hospitalization for each patient was deemed the index hospitalization.

In this sample, the average total direct cost incurred per patient during the index hospitalization after the initial 48-hour

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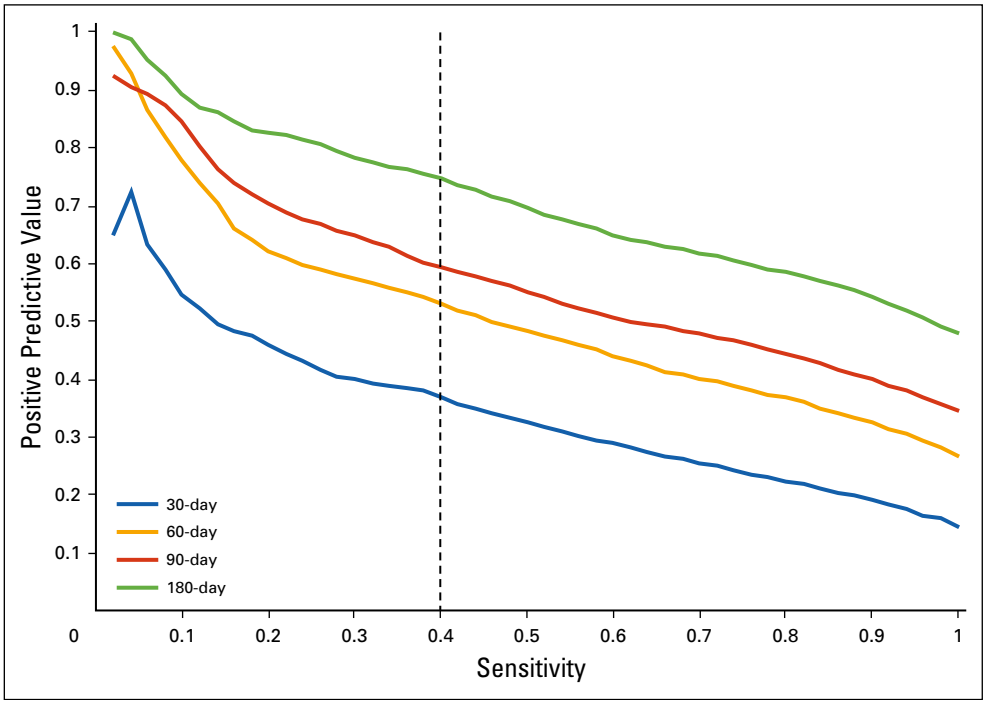

Fig 2. Average positive predictive value versus sensitivity for 30-, 60-, 90-, and 180-day mortality horizons. The average value is taken across the 20 test set splits.

assessment period was $7,495. The average direct costs of subsequent hospitalizations and outpatient visits totaled $9,194 and $1,172, respectively, per patient. We assume the total of these costs ($17,861; 95% CI, $9,162 to $21,665) to be potentially avoidable.

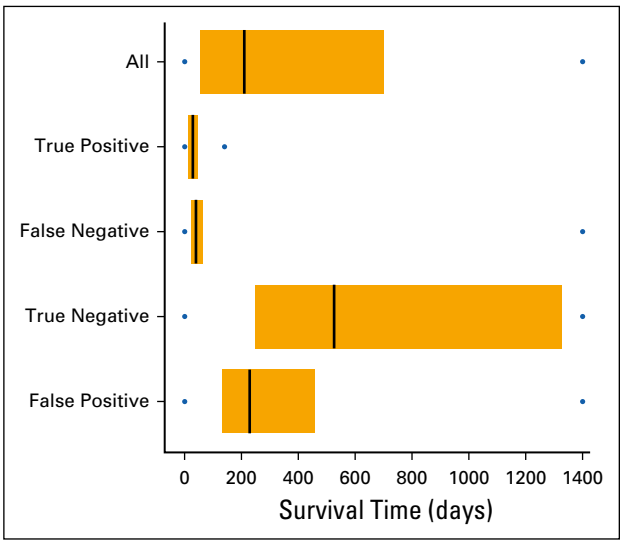

Fig 3. Box plots of the interquartile survival times for a specific test set. Using a 50% prediction threshold for classifying a visit as death likely within 90 days, the set is further subdivided into true positives, false negatives, true negatives, and false positives. The survival times are estimated by using the Kaplan-Meier curve to account for censoring among the latter two groups.

Had these 38 patients been treated under hospice care after the initial 48- hour assessment, it would have prevented 491 days of inpatient acute care, and the cost of hospice care would be $2,448 per patient. This implies a savings in this sample of $15,413 (95% CI, $9,162 to $21,665), that is, the potential avoidable cost ($17,861) minus the cost of hospice ($2,448).

One patient in our cohort is illustrative. On her first admission, the IMPAC would have predicted death within 90 days. This patient was discharged home with services and was readmitted twice. She subsequently underwent surgery, made multiple trips to the ICU, and eventually died in the hospital. Cost of care for this one patient after IMPAC 's prediction was $91,748 compared with $7,768 for equivalent days under hospice care after the index admission.

DISCUSSION

In the United States, end-of-life care is characterized by aggressive interventions, high rates of hospitalization, ICU admission, and ultimately death in the acute care setting.[5,26-28] Value-based payment programs like the Centers for Medicare

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& Medicaid Services' Oncology Care Model (which seek to reduce costs and improve quality) have focused on transitioning patients to hospice earlier, improving patients' prognostic understanding, and reducing hospitalizations. Reducing futile interventions in the last months of life is a significant opportunity for clinicians to improve the quality and value of health care. Multiple studies have demonstrated that patients who are well informed of their prognosis are less likely to receive aggressive interventions at the end of life.[29,30] Although patients rely on their oncologists for this information, physicians frequently overestimate life expectancy and inconsistently initiate goals-of-care discussions.

There are a few possible explanations for the observed pattern of end-of-life care at our center. Patients may seek more aggressive care at quaternary facilities because they are not yet ready to relinquish the hope of improved survival, which they associate, often inaccurately, with further disease-modifying care. On the providers' side, expertise and resources available at major centers may lead to greater use of treatments that are not standard elsewhere even when physicians may recognize poor prognosis. The availability of an objective prognostic tool, such as IMPAC embedded within the EHR system, could assist oncologists and patients in designing a more realistic plan of care.

IMPAC was tested by using different thresholds for the probability of death within a variety of life expectancies. Patients above the threshold would hypothetically be considered for less aggressive care. In this context, PPV is a performance measure preferred to specificity; mistakenly predicting that a patient is close to death is worse than predicting that he or she is not, because it could lead clinicians to inappropriately scale down care. Although the tool misidentified some patients as being likely to die within 90 days, the median survival of those was an additional 4.25 months, thus still flagging patients for whom a less aggressive approach should be considered. The patients that IMPAC incorrectly predicted to die within 90 days lived a total of 218 days (38 days longer than the 180-day hospice benefit.) It is possible that standard use of IMPAC could lead to an increase in patients outliving their hospice benefit. At this point, patients could resume Medicare insurance. It should be noted that in standard practice, overestimates of life expectancy (leading to late admission to hospice near to death) are common, as are underestimates (leading to patients outliving the 6-month hospice benefit). We believe an objective tool like IMPAC would improve both prognostic error types.

Our cost evaluation is based on the care received between the 48-hour time point and the actual death. We compared those costs with costs under hospice care for the same time period and estimated average savings of $15,413 per patient. The estimate is conservative because the total avoidable costs are limited to direct hospital costs, which do not include the cost of physician services, care provided outside of our system, or indirect hospital costs, and comparative hospice costs were based on payment rates, which are typically higher than actual costs.

There are several limitations to the assumptions used in this cost-avoidance estimate. First, we cannot ensure that all patients flagged by IMPAC would indeed switch to hospice care, or that it would occur exactly at 48 hours into the admission, or that hospice care would last for the remainder of the patient's life. Second, we needed to set a time point after the 48-hour IMPAC score and assume that the inpatient care and procedures would have been prevented if the patient had transferred to hospice. It is likely that some of the procedures received after the 48-hour IMPAC reading may have been performed with the goal of palliation. However, the use of costly palliative procedures is limited under the hospice benefit and is thus unlikely to significantly alter the cost avoidance estimates. Although this cost avoidance analysis has limitations, it does provide an estimate of the financial implications of a more rational approach to end-of-life care.

IMPAC uses data from the RI, which is a proprietary commercial product, thus limiting applicability at hospitals that do not use the RI. However, the RI is just one example of a high-frequency EHR-based patient health status index. When similar indices become more common in the future, our approach could be adapted to them as well.

In summary, we have developed a novel prognostic tool, IMPAC, that uses objective data to generate life expectancy probabilities automatically from EHR data in real time. If integrated into the standard clinical workflow, the IMPAC will signal oncologists that goals-of-care conversations are imperative, helping to facilitate prognostic understanding and informed decisions regarding downstream health care interventions. Our financial analysis quantified the potential reduction in avoidable care that better mortality predictions could achieve. Future work from this group will integrate IMPAC into the EHR and test the effect on prevalence of end-of-life conversations and use of downstream health care. JOP

Acknowledgment

The Yale Institutional Review Board approved this project prior to data collection.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Development of Imminent Mortality Predictor for Advanced Cancer (IMPAC), a Tool to Predict Short-Term Mortality in Hospitalized Patients With Advanced Cancer

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