Title

Predicting Emergency Visits and Hospital Admissions During Radiation and Chemoradiation: An Internally Validated Pretreatment Machine Learning Algorithm

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Predicting Emergency Visits and Hospital Admissions During Radiation and Chemoradiation: An Internally Validated Pretreatment Machine Learning Algorithm

abstract

Purpose Patients undergoing radiotherapy (RT) or chemoradiotherapy (CRT) may require emergency department evaluation or hospitalization. Early identification may direct preventative supportive care, improving outcomes and reducing health care costs. We developed and evaluated a machine learning (ML) approach to predict these events.

Methods A total of 8,134 outpatient courses of RT and CRT from a single institution from 2013 to 2016 were identified. Extensive pretreatment data were programmatically extracted and processed from the electronic health record (EHR). Training and internal validation cohorts were randomly generated (3:1 ratio). Gradient tree boosting (GTB), random forest, support vector machine, and least absolute shrinkage and selection operator logistic regression approaches were trained and internally validated based on area under receiver operating characteristic (AUROC) curve. The most predictive ML approach was also evaluated using only disease- and treatment-related factors to assess predictive gain of extensive EHR data.

Results All methods had high predictive accuracy, particularly GTB (validation AUROC, 0.798). Extensive EHR data beyond disease and treatment information improved accuracy (delta AUROC, 0.056). A Youden-based cutoff corresponded to validation sensitivity of 81.0% (175 of 216 courses with events) and specificity of 67.3% (1,218 of 1811 courses without events). Interpretability is an important advantage of GTB. Variable importance identified top predictive factors, including treatment (planned RT and systemic therapy), pretreatment encounters (emergency department visits and admissions in the year before treatment), vital signs (weight loss and pain score in the year before treatment), and laboratory values (albumin level at weeks before treatment).

Conclusion ML predicts emergency visits and hospitalization during cancer therapy. Incorporating predictions into clinical care algorithms may help direct personalized supportive care, improve quality of care, and reduce costs. A prospective trial investigating ML-assisted direction of increased clinical assessments during RT is planned.

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INTRODUCTION

An estimated 10% to 20% of patients with cancer undergoing outpatient radiotherapy (RT) or chemoradiotherapy (CRT) require emergency department (ED) evaluation or hospitalization because of symptoms from treatment, disease, or comorbidities, affecting treatment outcomes and health care costs.[1-6] During RT, patients are routinely seen weekly by their treating oncologists who often manage and triage acute health events. Identification of high-risk patients may direct supportive care and prevent such events,[2] and it has been estimated that approximately half of ED visits during cancer therapy are potentially preventable.[7] A recent literature review recommended identification of high-risk patients as a best practice to direct interventions and resources to reduce unplanned acute care for patients with cancer.[6] Given the predictive complexity of this actionable, unmet clinical need, there is an opportunity to leverage artificial intelligence and machine learning (ML), which has recently demonstrated successes in many areas of medicine.[8-12] ML and data processing techniques have increasingly gained traction as potential tools in the physician's clinical workflow

by synthesizing and processing large volumes of routine clinical data in the electronic health record (EHR) to form accurate predictions.[13-16]

Although various models, including ML algorithms based on EHR data, have been developed for addressing comparable problems in noncancer settings such as postoperative admission or hospital readmissions,[10,17-20] there have been no prior studies incorporating ML to predict such events during outpatient cancer therapy. The objective of this study was to create an algorithm with automated data processing and high-performance ML techniques[21] on routinely collected pretreatment EHR data to predict ED visits or hospitalization during RT or CRT. This could be implemented in real time in the clinic before or in parallel with treatment to direct personalized supportive care, improve quality of care, and reduce health care costs.

METHODS

This single-institution, retrospective cohort study was approved by the Duke University Medical Center Institutional Review Board (Pro00082776). All adult patients who underwent outpatient external-beam RT with or without concurrent systemic therapy (chemotherapy, immunotherapy, or hormonal therapy) from January 2013 to December 2016 were identified. Total-body irradiation was excluded, given planned admission for transplantation.

ML models were trained to identify the occurrence of any ED visit or hospitalization from day 2 of RT to the completion of RT in each course of CRT or RT alone. A fixed temporal end point (i.e., 30-day admission rate from the start of treatment) was considered to normalize for the increased opportunity of admission with longer treatments. However, the clinical objective of our algorithm was to maximize on-treatment clinical management to prevent both emergency visits or hospitalizations during the full duration of therapy. All emergency evaluations and hospital admissions were included, cancer and noncancer related, given that treating oncologists are typically the primary providers during therapy and manage or triage other comorbidities. Planned admissions for systemic therapy were excluded.

Data Source and Processing

The Duke Enterprise Data Unified Content Explorer was used to extract pretreatment EHR data from the institutional data warehouse (Table 1),[22] including demographics, vital signs, laboratory values, medications, health care encounters (including ED visits and hospitalizations), and medical history on the basis of the International Classification of Diseases (ninth and tenth revisions [ICD-9 and ICD-10]) codes.

ICD diagnosis codes were unified by converting ICD-9 to ICD-10 with the 2018 Centers for Disease Control and Prevention General Equivalence Mappings and consolidated into diagnosis subchapters.[23,24] Subchapters are reflective of broader disease categories, such as malignant neoplasm of digestive organs or malignant neoplasms of the lip, oral cavity, and pharynx. Medication names were unified into standard RxNorm names and Medical Subject Headings pharmacologic action classes with the National Library of Medicine RxMix.[25] Agency for Healthcare Research and Quality categories were used to define procedures. Vital sign data from the year before treatment were summarized into a priori physician-defined parameters, including weight loss from maximum weight and presence of hypertension, hypotension, tachycardia, bradycardia, hypoxemia, fever, or pain score of ≥ 4. All patients had baseline data, including demographics, disease and treatment, and social history variables. To represent the amount of data for patients before their radiation, duration and density of encounters (encounters per 100 days) in the EHR before RT were also assessed for each course.[26]

Treatment information included treated disease diagnosis (by subchapter and three-digit codes, with the exception of metastases, which were included as full codes to differentiate site), RT technique (2D, 3D conformal RT, intensity-modulated RT, stereotactic radiosurgery, stereotactic body RT, total skin irradiation), planned RT dose and number of fractions, concurrent systemic therapy (given in the first 2 weeks of RT), and recent systemic therapy (given in the 6 months before RT but not concurrently). Systemic agents were identified by the Medical Subject Headings pharmacologic action antineoplastic class, which was physician-reviewed for appropriate agents.

Table 1. Variables Used to Train Machine Learning Algorithms

Variable	No. of Levels or Variables
Demographic	
Sex (male, female)	2
Race	12
Age at start of treatment	Continuous
Ethnic group	8
Marital status	7
Religion	46
Zip code	1,248
Disease and treatment	
Primary treatment diagnosis (by subchapter/by three-digit ICD code with metastatic sites based on full ICD code)	59/172
Planned RT dose (Gy)	Continuous
Planned No. of RT fractions	Continuous
RT techniques used (2D or 3D conformal RT, intensity-modulated RT or volumetric modulated arc therapy, stereotactic radiosurgery/stereotactic body RT, total skin irradiation)	5
Any concurrent antineoplastic drugs (first 2 weeks of radiation)	Indicator
Concurrent antineoplastic drugs by MeSHPA class/RxNorm agent	51/86
Any recent antineoplastic drugs (6 months before radiation)	Indicator
Recent antineoplastic drugs by MeSHPA class/RxNorm agent	58/109
Treating radiation oncologist	26
Recent encounters before treatment in EHR	
Time since most recent admission and emergency visit before start of radiation	Continuous
No. of admissions in the month and year before start of radiation	Continuous
No. of days admitted in the year before start of radiation	Continuous
No. of emergency visits in the month and year before start of radiation	Continuous
Started RT as inpatient	Indicator
Medical history known at start of radiation	
All prior diagnosis and problem list ICD history (by ICD subchapter)	269
All prior CPT history	9,236
All prior level-3 Agency for Healthcare Research and Quality category history	323
Medications before and at start of therapy	
All recent medications (6 months before radiation; MeSHPA class)	298
All active medications at start of radiation (MeSHPA class)	295
Social history	
Reported tobacco use	5
Reported alcohol use	3
Reported illicit drug use	3
Reported sexually active	4
Recent laboratory values	
Presence of any abnormally flagged laboratory studies in the 4 weeks before start of radiation	737
Recent vital signs in the year before start of treatment	
Weight loss from maximum weight	Continuous
Presence of hypertension (SBP ≥ 130 mm Hg, DBP ≥ 80 mm Hg)	Indicator
Presence of hypotension (SBP < 90 mm Hg, DBP < 60 mm Hg)	Indicator

(Continued on following page)

Table 1. Variables Used to Train Machine Learning Algorithms (Continued)

Variable	No. of Levels or Variables
Presence of tachycardia (HR > 100 BPM)	Indicator
Presence of bradycardia (HR < 50 BPM)	Indicator
Presence of hypoxemia (O2 saturation ≤ 90)	Indicator
Presence of fever (temperature ≥ 38°C)	Indicator
Presence of pain score of ≥ 4 out of 10	Indicator

Abbreviations: BPM, beats per minute; CPT, Current Procedural Terminology; DBP, diastolic blood pressure; EHR, electronic health record; HR, heart rate; ICD, International Classification of Diseases; MeSHPA, Medical Subject Headings pharmacologic actions; RT, radiotherapy; SBP, systolic blood pressure.

Machine Learning

Training (6,107 courses; 75%) and testing (2,027 courses; 25%) cohorts were randomly generated preserving the proportion of events for major treated diseases.[27] Training and testing cohorts are separated subsets of the study population to allow model generation in the former and separate validation in the latter. Gradient tree boosting (GTB),[28] random forests,[29] and support vector machine (SVM)[30] were trained on the training set and evaluated on the testing cohort by the area under the receiver operating characteristic curve (AUROC).[29] For comparison, logistic regression using least absolute shrinkage and selection operator (LASSO) was also performed, which uses regularization to select a subset of the expansive set of available variables to generate a logistic regression model.[31] Low variance variables (ratio of most common to second most common values over 95:5 and percentage of unique values less than 10%) were removed from ML training inputs.[27] Hyperparameters for GTB were tuned by five-fold cross validation and SVM inputs were preprocessed by centering, and scaling. LASSO logistic regression was performed with 10-fold cross validation.

To assess the predictive benefit of extensive EHR data, the ML approach with greatest AUROC was used to compute a model with only disease and treatment-related variables (Table 1). GTB variable importance, the relative improvement in accuracy by the addition of each variable, was assessed.[28] In addition, the ML approach with greatest AUROC was also assessed by incorporating variables reflecting the duration and density of encounters in the EHR before treatment.

Cutoffs for ML models can be selected based on preferred trade-offs between sensitivity and specificity. For the purposes of this study, potential candidate cutoffs and corresponding sensitivity and specificity were calculated for the model with highest AUROC on the basis of the Youden J statistic and top-left approaches.[32,33] On the basis of these candidate cutoffs, false positives and negatives were inspected for gross patterns in major variables.

Calibration of the model with the highest AUROC was also evaluated using the Hosmer-Lemeshow test, as well as visual inspection of the correlation plot using deciles of fitted risk values in the testing cohort.[34] Analyses were performed in R version 3.3.2 (R Foundation).[23,28-30] Up-to-date source code is available online.[35,36]

RESULTS

A total of 8,134 RT courses for 6,879 patients were identified (Table 2). The most common treatment courses were to any metastatic site (2,032; of which 1,206 were brain metastases), followed by primary thoracic (1,092) and breast (1,080) cancers. Most courses were for female patients (54%), 27% included concurrent systemic therapy, and 28% included recent systemic therapy. Admissions or emergency visits occurred during 878 courses (11%). There was a wide range of EHR history before the start of RT (median, 64.0 months; IQR, 7.0 to 177.0 months). Similarly, there was a wide range of density of encounters per 100 days (median, 4.9; IQR, 1.9 to 20.4).

Internal validation indicated that all ML techniques generated strong predictive models, although the GTB model (AUROC, 0.798) had greater AUROC than random forests (0.770), SVM (0.759), and LASSO logistic regression (0.768). All had greater AUROC compared with the GTB trained exclusively on disease and treatment-related variables (AUROC, 0.742; Fig 1).

Table 2. Major Characteristics of Training and Validation Cohorts (per course)

Characteristic	Total (n = 8,134)	Training (n = 6,107)	Validation (n = 2,027)
Sex, No. (%)			
Male	3,714 (46)	2,805 (46)	909 (45)
Female	4,420 (54)	3,302 (54)	1,118 (55)
Median age, years (IQR)	63.1 (53.3-70.9)	63.0 (53.4-70.8	63.3 (53.1-71.3)
Race, No. (%)*			
White	6,038 (74)	4,516 (74)	1,522 (75)
Black	1,598 (20)	1,209 (20)	389 (19)
Other	498 (6)	382 (6)	116 (6)
Total distinct patients, No.	6,879	5,383	1,908
Courses with admissions or emergency visits, No. (%)	878 (11)	662 (11)	216 (11)
Admission only	207 (3)	157 (3)	50 (2)
Emergency visit only	292 (4)	213 (3)	79 (4)
Both admission and emergency visit	379 (5)	292 (5)	87 (4)
Select disease sites, No. (%)			
Brain metastases	1,206 (15)	898 (15)	308 (15)
Respiratory/intrathoracic cancer	1,092 (13)	822 (13)	270 (13)
Breast cancer	1,080 (13)	818 (13)	262 (13)
GI cancer	908 (11)	680 (11)	228 (11)
Bone metastases	830 (10)	629 (10)	201 (10)
Genitourinary cancer	336 (3)	260 (4)	76 (4)
Gynecologic cancer	264 (3)	200 (3)	64 (3)
Lip, oral cavity, pharynx cancers	242 (3)	183 (3)	59 (3)
Systemic therapy, No. (%)			
Recent systemic therapy	2,311 (28)	1,722 (28)	589 (29)
Concurrent systemic therapy	2,176 (27)	1,635 (27)	541 (27)
EHR history before RT			
Median duration, months (IQR)	64.0 (7.0-177.0)	64.4 (6.6-177.0)	62.7 (8.3-177.0)
Median encounters per 100 days, No. (IQR)	4.9 (1.9-20.4)	5.0 (1.9-20.4)	4.8 (1.9-20.6)

Abbreviations: EHR, electronic health record; IQR, interquartile range; RT, radiotherapy
*EHR uses 12 distinct values for race that were used to train machine learning models.

Candidate cutoffs for GTB were 81.0% sensitive and 67.3% specific by the Youden approach and 75.0% sensitive and 73.4% specific by the top-left approach. The Youden cutoff corresponded to accurate prediction of 175 of 216 courses resulting in ED encounters or admissions and 1,218 of 1,811 courses without an event in the validation set. The top-left cutoff reflected accurate prediction of 162 of 216 courses resulting in an event and 1,330 of 1,811 without an event.

GTB relative variable importance showed relative predictive gain from the inclusion of diverse EHR data. The variables providing the greatest contribution to predictive accuracy included treatment factors (planned radiation dose and number of fractions, concurrent systemic therapy) and pretreatment encounters (number and recentness of ED visits and admissions), vitals (weight loss and pain score), and laboratory values (albumin; Fig 2). Among these, no variables individually accounted for more than 7.5% of the model. The comparison LASSO logistic regression model indicated similar predictive variables. GI malignancies were over-represented among false positives compared with other disease sites. EHR encounter history duration and density as variables did not affect model performance and were omitted in the final model. Assessment of calibration with the Hosmer-Lemeshow test and visualization of the calibration plot for the GTB model suggested no evidence of poor calibration ($P = .21$; Fig 3).

DISCUSSION

Our internally validated ML algorithm trained on pretreatment and treatment parameters had high predictive value for ED evaluation or admission during outpatient cancer therapy and compared favorably with readmission and postsurgical admission models.[10,17-20] This automated, personalized approach may be quickly implemented and trained using institution-specific data with minimal manual data curation to help physicians optimize supportive care, which may improve outcomes and reduce health care costs.[1,2,6,13] This could be applied before or in parallel with treatment to identify patients who may benefit from more aggressive supportive care during their routine management to mitigate a high rate of potentially preventable hospital encounters.[2,6,7]

Prior early data suggest that increased frequency of routine assessment by implementing a symptom management clinic in unselected patients undergoing RT for head and neck cancer reduces the frequency of emergency visits and hospitalization.[2] In a clinical setting, our algorithm would be implemented in an automated fashion to assign an acute risk probability to patients. Patients with higher probability would be selected for a directed program with more frequent clinical evaluation. This personalized care would reduce overall costs by preventing acute care. In addition, although we present candidate cutoffs on the basis of Youden and top-left approaches, the threshold for designating high-risk patients could be institution specific, allowing clinics to balance sensitivity and specificity on the basis of clinical judgment or available resources. Calibration suggests that estimated risk of an acute event by our model is consistent with outcome and thus could also be incorporated into clinical judgment. Study of the clinical results of ML-directed intervention is the objective of a planned clinical trial.

A number of studies have recently applied artificial intelligence and ML to classification questions in other medical subspecialties, with high predictive accuracy.[8-12] Among these, Rajkomar et al[10] described the use of ML on EHR data to predict clinically relevant end points in admitted patients, including 30-day unplanned readmission (AUROC, 0.75 to 0.76). To our knowledge, our data represent the first application of ML to assessing emergency evaluation or hospitalization risk in patients undergoing outpatient cancer therapy. Prior ML models in oncology have focused on RT-associated toxicities on the basis of normal tissue doses[37-42] or clinical decline of admitted patients with hematologic malignancies.[43] Non-ML models of acute events during cancer therapy have been developed for chemotherapy toxicity.[44-48] The most comparable prior study was the development of a logistic regression model on the basis of more labor-intensive, manually curated data predicting chemotherapy-related hospitalization in patients undergoing palliative chemotherapy, with an AUROC of 0.71.[48] Overall, our internally validated results in this distinct clinical question compare favorably with prior work.

Although ML interpretation is limited because of complex nonlinear and interacting relationships and the presence of correlated factors, inclusion of extensive noncancer variables improved accuracy. In contrast to more black box methods, GTB has the advantage of balancing strong predictive ability with assessment of relative variable importance. This allows for the calculation of the predictive benefit of incorporating each variable. In addition to disease and treatment-related variables such as planned RT fractions and dose and concurrent systemic therapy, variable importance also identified pretreatment encounters (ED and admissions history), vital signs (weight loss and pain score), and abnormal

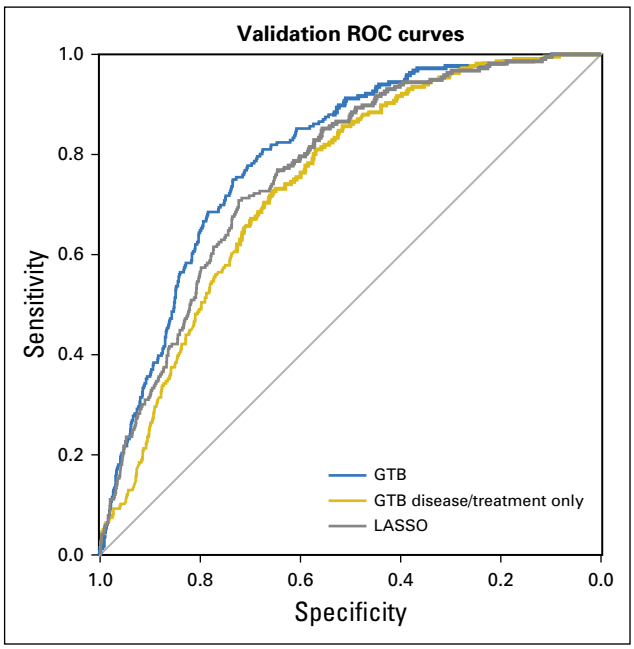


Fig 1. Validation receiver operating characteristic (ROC) curves for machine learning techniques. Although all three methods yielded strong predictive results, gradient boosted trees (GTB; 0.798) had greater area under the ROC curve than random forest (0.770; not shown), support vector machine (0.759; not shown), and least absolute shrinkage and selection operator (LASSO) logistic regression (0.768) methods. All had greater area under the ROC curve compared with GTB trained on only disease and treatment-related characteristics (0.742).

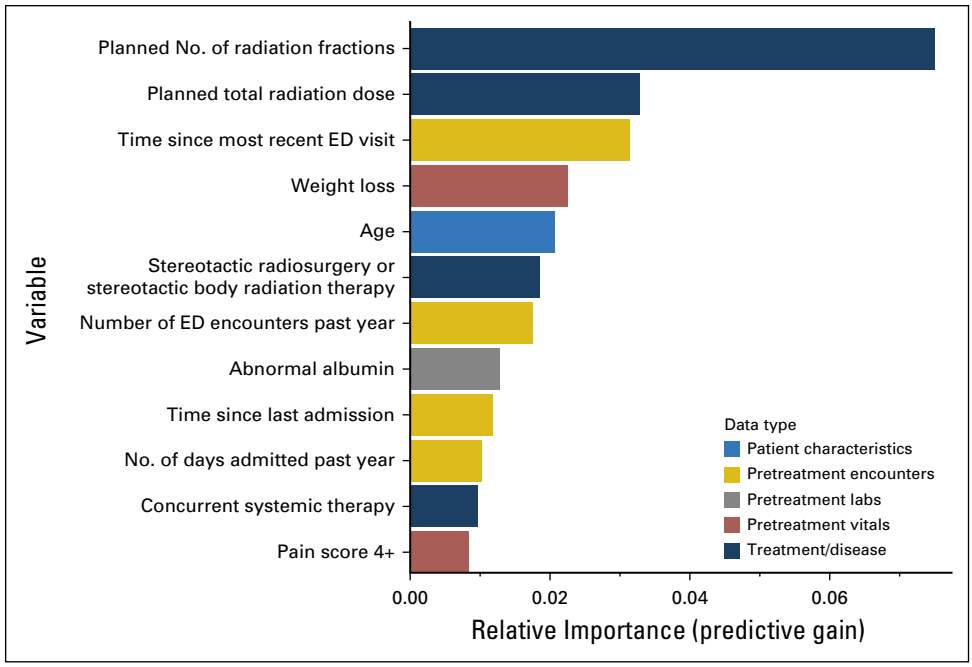
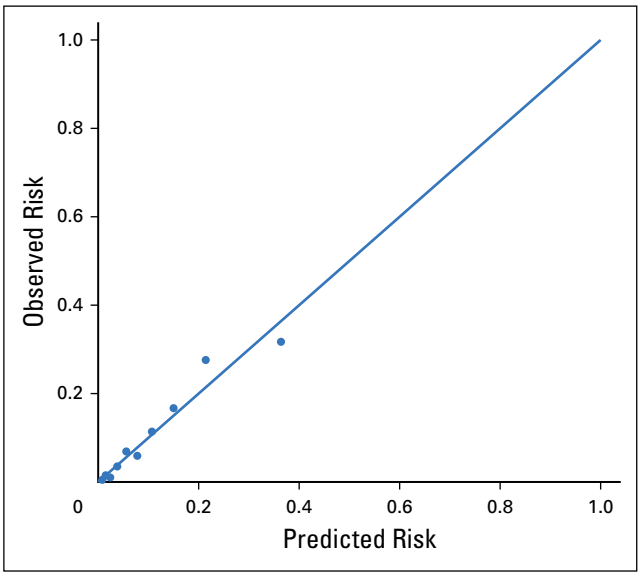


Fig 2. Variable importance for the top predictive gradient tree boosting predictive variables. These included treatment factors (planned radiation dose and number of fractions, concurrent systemic therapy) and pretreatment encounters (number of and recentness of emergency department [ED] visits and admissions in the year before treatment), vitals (weight loss and pain score in the year before treatment), and laboratory values (abnormal albumin in the 4 weeks before treatment).

laboratory values (albumin) as major contributors to prediction. No individual variables dominated the model. Planned RT dose and number of fractions likely reflect a combination of both treatment intensity as well as a greater opportunity window for admission or emergency evaluation and thus emphasize the importance of active management in patients who may undergo a long treatment course. Our algorithm includes and approximates previously described associated clinical variables associated with admissions.[1] It is important to reiterate that these variables may have correlative relationships with other variables and often a complex nonlinear relationship with the rate of events. For example, specific treatment regimens and diseases are highly correlated. Thus, cautious interpretation of ML models is best practice. It was also grossly observed that there was a higher representation of GI malignancies among the false positives. This may reflect patient heterogeneity or importance of potentially uncaptured variables in a disease with high admission rates.

Fig 3. Validation calibration plot for the gradient tree boosting model. Assessment with the Hosmer-Lemeshow test suggested no evidence of poor calibration ($P = .21$).



This study is potentially limited by underascertainment of emergency visits or hospital admissions given that only data from a single health care system was available. This may reduce the sensitivity of the model (by missing patients who experienced an event at an outside institution). However, Duke's catchment net spans multiple facilities that share a single EHR across a wide geographic area. Moreover, RT, by nature of its daily treatments, is geographically limiting. Given this, our representation of admissions is likely greater compared with prior studies using a broader population, which may be more prone to admissions outside of the studied hospital system.[18,19] In addition, we were unable to compare model performance with gold standard clinician evaluation. Retrospective review of patient records to generate physician-based assessment of admission risk would likely be inaccurate, given the lack of the feasibility of a true clinical assessment. However, ROC results compare

favorably with prior models in other medical specialties.[10,17-20] Comparison with clinician evaluation and the clinical impact of increased clinical assessments during treatment are components of a planned prospective clinical trial.

The potential external accuracy of the model, although strong in our internal validation cohort, may be limited by the structure of data, as automated data extraction requires diagnoses, laboratory tests, and medications conformable to unified terminology. It is also possible that data that are systematically collected in other clinical settings may incrementally improve on our predictive accuracy (such as treatment intent, which is not consistently documented in our data). Similarly, data structure may vary institutionally, potentially limiting generalizability of the specific model. Sufficient similarity, however, would allow individual institutions to apply our algorithm to institution-specific data, and we have made our source code available online.[35,36] Finally, it may be difficult to predict how altering cancer therapy treatment recommendations themselves may alter a patient's risk of acute events; thus, we favor applying the model to direct supportive care.

External validation is required to fully assess our model. This is currently planned at an outside institution in an alternate EHR system. Future work will include iterative improvements through the incorporation of additional variables, including those obtained by the application of natural language processing to clinical text. Future updates will continue to be available online.[35,36] A prospective clinical trial investigating ML-assisted direction of increased clinical assessments during cancer treatment is planned to assess both model accuracy and clinical impact. In addition, prospective data would enable the opportunity to identify which acute visits are potentially preventable, which remains a clinical need.[7]

In conclusion, ML offers accurate predictions of emergency evaluation and hospital admission during outpatient cancer therapy. Incorporation of these predictions into clinical care may direct personalized care to improve the quality of care and reduce health care costs.

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Manuscript writing: All authors
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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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