ARTIFICIAL INTELLIGENCE

original reports abstract

Machine Learning Applied to Electronic Health Records: Identification of Chemotherapy Patients at High Risk for Preventable Emergency Department Visits and Hospital Admissions

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PURPOSE Acute care use (ACU) is a major driver of oncologic costs and is penalized by a Centers for Medicare & Medicaid Services quality measure, OP-35. Targeted interventions reduce preventable ACU; however, identifying which patients might benefit remains challenging. Prior predictive models have made use of a limited subset of the data in the electronic health record (EHR). We aimed to predict risk of preventable ACU after starting chemotherapy using machine learning (ML) algorithms trained on comprehensive EHR data.

METHODS Chemotherapy patients treated at an academic institution and affiliated community care sites between January 2013 and July 2019 who met inclusion criteria for OP-35 were identified. Preventable ACU was defined using OP-35 criteria. Structured EHR data generated before chemotherapy treatment were obtained. ML models were trained to predict risk for ACU after starting chemotherapy using 80% of the cohort. The remaining 20% were used to test model performance by the area under the receiver operator curve.

RESULTS Eight thousand four hundred thirty-nine patients were included, of whom 35% had preventable ACU within 180 days of starting chemotherapy. Our primary model classified patients at risk for preventable ACU with an area under the receiver operator curve of 0.783 (95% CI, 0.761 to 0.806). Performance was better for identifying admissions than emergency department visits. Key variables included prior hospitalizations, cancer stage, race, laboratory values, and a diagnosis of depression. Analyses showed limited benefit from including patient-reported outcome data and indicated inequities in outcomes and risk modeling for Black and Medicaid patients.

CONCLUSION Dense EHR data can identify patients at risk for ACU using ML with promising accuracy. These models have potential to improve cancer care outcomes, patient experience, and costs by allowing for targeted, preventative interventions.

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INTRODUCTION

Acute care use (ACU) including emergency department (ED) visits and inpatient (IP) admissions account for nearly half of the cost associated with oncologic care in the United States.[1,2] As many as 50% of these visits are potentially preventable with early outpatient interventions.[3-6] Furthermore, substantial regional variation in the costs and frequency of ACU suggest opportunities for reduction of ACU.[1,7] Not only is ACU costly, unplanned ACU negatively affects patient quality of life and is poor-quality care.[8,9] In an effort to improve quality of care, increase transparency, and reduce costs, the Centers for Medicare & Medicaid Services (CMS) implemented a new quality measure, Chemotherapy Measure (OP-35), which tracks IP admissions or ED visits for patients age ≥ 18 years for potentially preventable diagnoses within 30 days of outpatient chemotherapy administration.[10]

Although many of these admissions or ED visits are avoidable with adequate preventative care, resource constraints necessitate preventative interventions to be targeted. Therefore, developing a robust, data-driven method to identify patients who are most at risk of ED visits or acute admissions at the time of chemotherapy initiation would be valuable for health systems seeking to improve performance on OP-35 metrics. In addition, risk-stratifying patients according to their likelihood of ACU would prioritize preventative care to patients most in need, improving patient outcomes, comfort, and satisfaction during a chemotherapy regimen. Artificial intelligence (AI), including machine learning (ML) has potential to provide this type of risk assessment to physicians.

AI-driven oncologic care includes deriving novel insights from complex health data to predict patient outcomes, including cancer survival.[11,12] Regulatory changes have also demanded the use of real-world

ASSOCIATED CONTENT

Appendix

Author affiliations and support information (if applicable) appear at the end of this article.

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CONTEXT

Key Objective

To predict risk for preventable acute care use (ACU) after starting chemotherapy using comprehensive structured electronic health record (EHR) data.

Knowledge Generated

We evaluated several machine learning models to predict ACU following chemotherapy using a comprehensive capture of pretreatment structured variables from the EHR. The top-performing model achieved strong performance (area under the receiver operator curve = 0.783; 95% CI, 0.761 to 0.806) and identified known and previously underutilized features associated with ACU, including prior hospitalization and diagnosis of depression. We found inequities in outcomes and risk predictions for Black and Medicaid patients, suggesting closer monitoring could help achieve equitable outcomes for these groups.

Relevance

Patients at risk for preventable ACU after starting chemotherapy can be identified using machine learning. Models could risk-stratify patients using systematically captured EHR data, providing opportunities for clinical decision support tools to help health systems deliver targeted, preventative interventions to improve patient outcomes.

data, such as that derived from electronic health records (EHRs), to guide clinical assertions and practice guidelines.[13] ML applied to EHRs has been used specifically to tackle the issue of identifying patients with cancer at risk for ACU.[14-17] Although these studies advance our knowledge in the field, they were limited to a small number of available variables in the EHR, used logistic regression instead of more robust AI models, and/or did not use OP-35 criteria to determine preventable ACU.

As AI enables better use of real-world data, there is an opportunity to develop clinical decision support tools that could help identify patients at higher risk of ACU following chemotherapy and therefore improve clinical and patient outcomes among these patients. We hypothesized that we could accurately identify patients with cancer undergoing chemotherapy who are at risk of preventable ACU, as defined by CMS's OP-35 using prechemotherapy EHR data. We developed, validated, and compared nine ML models to predict ACU at 3, 6, and 12 months following the start of chemotherapy among patients seen in oncology clinics affiliated with a large academic cancer center (Fig 1A). We also incorporated patient-reported outcomes (PROs) to evaluate the impact of these data on predicting risk for preventable ACU.

METHODS

Setting

This retrospective, prognostic cohort study was performed at a Comprehensive Cancer Center (CCC). The CCC includes a large tertiary practice, as well as a community hospital and community practices. This study followed the Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis and Minimum Information for Medical AI Reporting guidelines.[18,19] This study was approved by the university's institutional review board with a waiver of informed consent. The study was approved by the local ethics committee.

Study Population

Adult patients with cancer were eligible for this study if they underwent chemotherapy at the CCC between January 1, 2013, and July 10, 2019 (Fig 1B). Patients were excluded if they failed to meet inclusion criteria for OP-35 (n = 2,272), on the basis of CMS's 2019 Chemotherapy Measure Updates and Specifications Report.[20] To limit effects because of loss to follow-up, patients who did not have an encounter after their episode of care, defined by the 180 days after the start of chemotherapy, or with a recorded date of death within the episode of care without record of ACU were excluded (n = 1,217). Finally, patients were excluded if they had no vitals, laboratory, medication, diagnosis, and/or procedural data from the 180 days before chemotherapy (n = 1,237).

Study Variables

All clinical data were obtained from the EHR. The CCC has a fully implemented EPIC EHR system, installed in 2008, that includes demographic, social, vital sign, procedure, diagnosis, medication, laboratory, health care utilization, and cancer-specific data generated before the first date of chemotherapy.[21] Patient demographics and clinical data were captured at the time of diagnosis and first date of treatment, including age at treatment, primary cancer type, sex, insurance payor at treatment, ethnicity, race, and stage at diagnosis. Charlson comorbidity score was calculated for each patient on the basis of pretreatment diagnoses. Deaths were captured from the internal Cancer Registry or from the patient health records. To limit data leakage allowing the models to learn from future events, data generated after patients' first date of chemotherapy treatment were only used for cohort building and determining

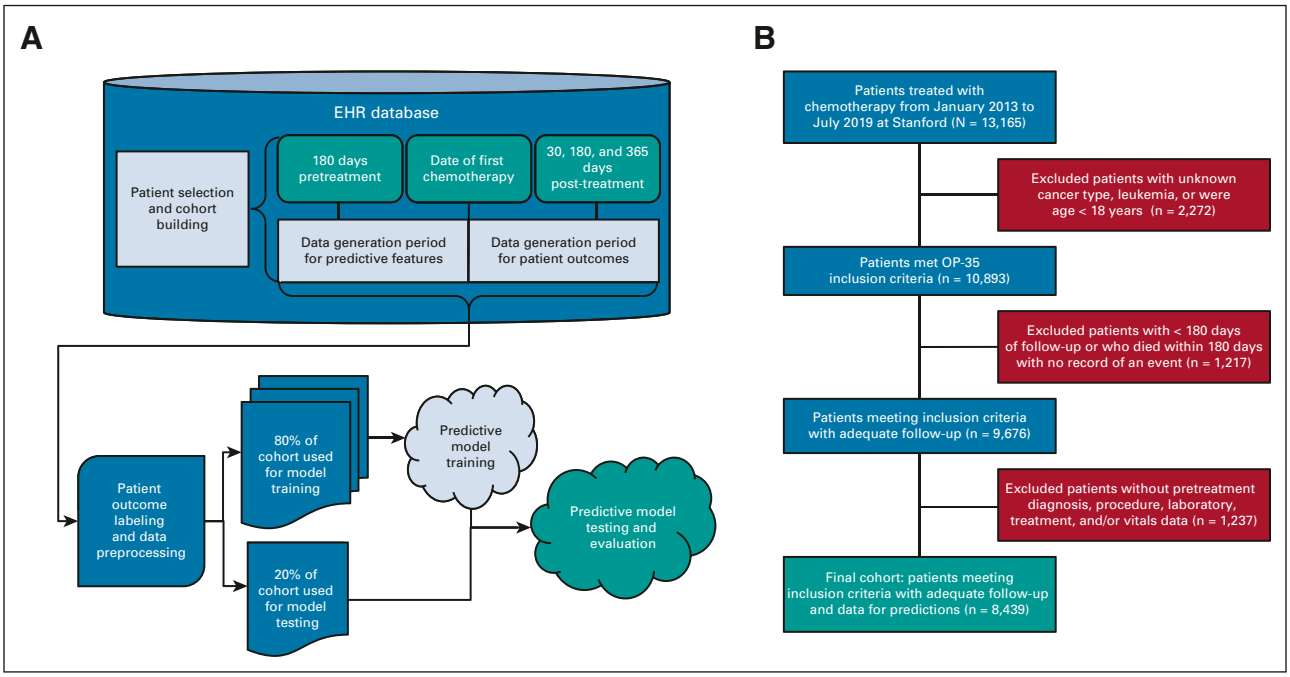

FIG 1. Study design and flow diagram. (A) Comprehensive EHR data on patients who met our inclusion criteria were obtained from our database. Data generated 180 days before the start of chemotherapy were processed and used to train machine learning models to predict risk of preventable ACU. Data generated after chemotherapy initiation were used to determine patient outcomes. (B) Inclusion criteria included OP-35 denominator inclusion criteria, follow-up 180 days after the episode of care for patients who did not have ACU, and adequate data to make predictions. ACU, acute care use; EHR, electronic health record.

patient outcomes and otherwise were not included in any training or testing data provided to the models. Additionally, training data were limited to information generated in the 180 days before chemotherapy initiation. Further details on data cleaning and preprocessing are available in the Appendix 1.

Outcome Measures

Although CMS uses a 30-day time frame for OP-35 numerator inclusion, our primary outcome was a hospitalization or ED visit that met OP-35 criteria (OP-35 events) within the episode of care (180 days) following the initiation of chemotherapy. However, to test model sensitivities, we analyzed performance at 30, 180, and 365 days after chemotherapy initiation and additionally analyzed for ED-only and IP-only events. ED visits resulting in admission were treated as IP events.

Predictive Models

Patients were randomly assigned to be in the training (80%) or testing cohort (20%). To predict hospitalization or ED visits following chemotherapy initiation, nine models were developed: logistic regression with least absolute shrinkage and selection operator (LASSO), Ridge, and Elastic Net penalties; random forests; gradient-boosted trees; multilayer perceptron neural networks; support vector machines; K Nearest Neighbors classifiers; and ensemble voting models that used equal voting on the predictions from other models. Additional details of model building, training, and selection are included in the Appendix 1.

Evaluation Metrics

To evaluate model performance, the models were validated on the 20% test set, not used previously for model development, on the basis of the area under the receiver operator curve (AUROC) with 1,000-fold bootstrap to determine CIs.

Patient-Reported Outcome Subanalysis

A subanalysis was performed on patients with at least one 12-item Patient-Reported Outcomes Measurement Information System (PROMIS) survey completed within 180 days before starting chemotherapy.[22,23] Two new models were trained on this cohort using same preprocessing, model training, and evaluation steps described above: one with the original features, and a second with the inclusion of 14 features derived from the PROMIS data (12-item survey responses, and the global mental and physical health scores).[24]

Evaluation of Disparities in the Model Output

To determine any effect of inherent bias in our models and data, patients were stratified in the testing cohort by their race, ethnicity, and insurance status, and then, their predicted risk-score percentiles were compared with their true rates of OP-35 events. Empiric cumulative distributions of predicted risk-score percentiles for subgroups were

plotted against each other to assess how the models predicted each subgroup's risk for OP-35 events.

Statistical Analysis

Patient clinical characteristics were compared using univariable odds ratios (ORs). The results are presented as mean ± standard deviation, unless otherwise noted.

RESULTS

Cohort Characteristics

A total of 8,439 patients were included in the study cohort who were, on average, age 60.42 (14.48) years, 50% female, and 45% non-White (Table 1). A total of 2,939 patients (35%) met our primary outcome of having at least one OP-35 event within the first 180 days after starting chemotherapy (Appendix Fig A1A). OP-35 events decreased in frequency the further from chemotherapy initiation (Appendix Fig A1B). The most common diagnoses associated with these events included pain, complications of bone marrow suppression, such as neutropenia and sepsis, and gastrointestinal side effects, such as emesis (Appendix Fig A1C).

Patients with OP-35 events by 180 days significantly varied in multiple clinical characteristics than those without. For instance, these patients were on average 2.5 years younger at diagnosis (OR 0.988 per year; 95% CI, 0.985 to 0.991; $P < .0001$), more likely to be male (OR 1.113; 95% CI, 1.102 to 1.123; $P < .0001$), non-White (OR 1.280; 95% CI, 1.252 to 1.309; $P < .0001$), have stage IV disease (OR 1.873; 95% CI, 1.762 to 1.993; $P < .0001$), have a smoking history (OR 1.056; 95% CI, 1.062 to 1.051; $P < .0001$), and have a diagnosis of depression (OR 1.422; 95% CI, 1.369 to 1.478; $P < .0001$).

Model Performance for Predicting Risk of OP-35 Events

Overall, the various ML models performed reasonably well for determining patient risk for OP-35 events using the 759 EHR-based variables on which they were trained (AUROC range: 0.740-0.806, Appendix Table A2). Although the ensemble voting model had the best performance for predicting events by 180 days (AUROC 0.806; 95% CI, 0.794 to 0.816), the LASSO model performed comparably (AUROC 0.783; 95% CI, 0.761 to 0.806; AUROC range during cross-validation = 0.746-0.825, Appendix Figs 2B and 2C). As LASSO is a regularized form of logistic regression, it is easier to interpret how it is making predictions than with more complicated models and was therefore chosen to be our primary model. Although thresholds to label if a patient is likely to have an event could vary depending on the clinical use case, at Youden's index (probability of event = .278), this model had the following performance metrics: accuracy = 0.700; F1 score = 0.644; precision (event) = 0.567; precision (nonevent) = 0.821; recall (event) = 0.745; recall (nonevent) = 0.821; and area under the precision-recall curve = 0.702. This model selected 125 of 759 possible features to use in its predictions. These features included clinical variables used in prior risk models, such as the number of pretreatment hospitalizations, advanced stage disease, and white blood cell count, as well as underutilized features, including a diagnosis of depression, race, and prior brainstem magnetic resonance imaging (see Table 2 for the top model features and Appendix Table A3 for the full feature set).

To test the model's discriminative power in a setting similar to how it might be implemented at the point of care, the testing cohort was stratified into high-, intermediate-, and low-risk groups on the basis of their predicted risk score tertile. Kaplan-Meier survival curves for OP-35 events showed good separation between risk groups (Fig 2, $P < .00001$ for each group by log-rank test). By 180 days after starting chemotherapy, 357 (64%) of the 563 high-risk patients had an OP-35 event, whereas 75 (13%) of the 563 low-risk patients had an event.

To assess the relative importance of each type of feature (eg, medications) on the model's predictions, performance was evaluated after retraining when withholding each feature type (Appendix Table A4). All 95% CIs for the AUROCs of the models with the withheld data overlapped with that of the model trained with the full data set; however, predictive performance generally declined when withholding feature types and experienced the greatest decline when withholding demographic and cancer-specific data (AUROC 0.779; 95% CI, 0.755 to 0.802).

Model Performance for Alternative Outcomes

The sensitivity of the primary LASSO model for predicting risk for OP-35 events was tested at alternative time points (30 and 365 days) and specific ACU setting (ED-only *v* IP-only). The performance decreased slightly compared with the 180-day outcome for both the 30-day (AUROC 0.774; 95% CI, 0.760 to 0.788) and 365-day outcomes (AUROC 0.772; 95% CI, 0.761 to 0.784; Appendix Fig A2A). The model had improved performance predicting IP-only events (AUROC 0.798; 95% CI, 0.787 to 0.809), but substantially worse performance for ED-only events (AUROC 0.615; 95% CI, 0.595 to 0.635) compared with the primary outcome; however, a model trained specifically to predict ED events performed comparably (AUROC 0.781; 95% CI, 0.762 to 0.796).

Effect of Race, Ethnicity, and Insurance Type

Notably, Black, Hispanic or Latino, and Medicaid patients were predicted to be disproportionately higher risk than their counterparts (Figs 3A-3C). For instance, 50% of the Black patients in our cohort were predicted to be at the 67.5th percentile of risk or higher. In the testing cohort, there was no significant difference in events between Black and White patients (41.3% *v* 33.5% with an event, respectively, $P = .275$); however, the predicted risk percentile for Black patients was significantly higher (64.15 ± 26.41 *v* 47.25 ± 28.59, $P = .0001$). Concordantly, the model also exhibited poor calibration for Black patients (Appendix Fig A3A). Similarly, 50% of Medicaid patients were predicted

TABLE 1. Patient Demographics

Patient Characteristic	Total Cohort (N = 8,439)	Patients With OP-35 Events by 180 Days (n = 2,939)	Patients Without OP-35 Events by 180 Days (n = 5,500)	OR (95% CI)	*P*
Age, No. (%)					
At diagnosis	58.65 (14.4)	57.02 (15.21)	59.53 (13.88)	0.988 (0.985 to 0.991)	< .0001
At first chemotherapy	60.42 (14.48)	58.72 (15.25)	61.33 (13.98)	0.988 (0.985 to 0.991)	< .0001
Sex, No. (%)					
Female	4,250 (50.4)	1,429 (48.6)	2,821 (51.3)	0.899 (0.890 to 0.907)	< .0001
Race, No. (%)					
White	4,630 (54.9)	1,495 (50.9)	3,135 (57.0)	0.781 (0.764 to 0.799)	< .0001
Asian	1897 (22.5)	669 (22.8)	1,228 (22.3)	1.025 (1.023 to 1.028)	< .0001
Black	233 (2.8)	116 (3.9)	117 (2.1)	1.891 (1.601 to 2.232)	< .0001
Other or Unknown	1,679 (19.9)	659 (22.4)	1,020 (18.5)	1.269 (1.237 to 1.303)	< .0001
Ethnicity, No. (%)					
Hispanic or Latino	1,094 (13.0)	453 (15.4)	641 (11.7)	1.381 (1.325 to 1.440)	< .0001
Non-Hispanic or non-Latino	7,231 (85.7)	2,477 (84.3)	4,754 (86.4)	0.841 (0.823 to 0.860)	< .0001
Other or unknown	114 (1.4)	9 (0.3)	105 (1.9)	0.158 (0.045 to 0.556)	.002
Cancer type, No. (%)					
Gastrointestinal	1,929 (22.9)	677 (23.0)	1,252 (22.8)	1.015 (1.014 to 1.017)	< .0001
Breast	1,383 (16.4)	294 (10.0)	1,089 (19.8)	0.450 (0.403 to 0.502)	< .0001
Lymphoma	1,175 (13.9)	718 (24.4)	457 (8.3)	3.567 (3.033 to 4.195)	< .0001
Genitourinary	1,165 (13.8)	269 (9.2)	896 (16.3)	0.518 (0.471 to 0.569)	< .0001
Thoracic	825 (9.8)	285 (9.7)	540 (9.8)	0.986 (0.984 to 0.988)	< .0001
Head and neck	697 (8.3)	228 (7.8)	469 (8.5)	0.902 (0.887 to 0.918)	< .0001
Gynecologic	562 (6.7)	196 (6.7)	366 (6.7)	1.002 (1.002 to 1.003)	< .0001
Other	703 (8.3)	272 (9.3)	431 (7.8)	1.199 (1.165 to 1.235)	< .0001
Cancer stage, No. (%)					
Stage I	1,432 (17.0)	368 (12.5)	1,064 (19.3)	0.597 (0.559 to 0.638)	< .0001
Stage II	1,679 (19.9)	438 (14.9)	1,241 (22.6)	0.601 (0.566 to 0.639)	< .0001
Stage III	1,168 (13.8)	482 (16.4)	686 (12.5)	1.377 (1.322 to 1.433)	< .0001
Stage IV	2,318 (27.5)	1,054 (35.9)	1,264 (23.0)	1.874 (1.762 to 1.993)	< .0001
Unknown	1,842 (21.8)	597 (20.3)	1,245 (22.6)	0.871 (0.858 to 0.884)	< .0001
Treatment details, No. (%)					
Time from diagnosis to chemotherapy, years	1.24 (2.21)	1.16 (2.08)	1.28 (2.27)	0.999 (0.999 to 1.000)	.0146
Palliative chemotherapy	795 (9.4)	357 (12.1)	438 (8.0)	1.598 (1.491 to 1.712)	< .0001
Insurance, No. (%)					
Medicare or Medicaid	3,955 (46.9)	1,318 (44.8)	2,637 (47.9)	0.883 (0.873 to 0.893)	< .0001
Private	3,049 (36.1)	1,119 (38.1)	1930 (35.1)	1.137 (1.124 to 1.151)	< .0001
Other or Unknown	1,435 (17.0)	502 (17.1)	933 (17.0)	1.008 (1.007 to 1.009)	< .0001
Smoking history, No. (%)					
Current or former smoker	3,151 (37.3)	1,122 (38.2)	2029 (36.9)	1.056 (1.051 to 1.062)	< .0001
Never smoker	4,983 (59.0)	1718 (58.5)	3,265 (59.4)	0.963 (0.960 to 0.966)	< .0001
Unknown	305 (3.6)	99 (3.4)	206 (3.7)	0.896 (0.872 to 0.920)	< .0001
Comorbidities, No. (%)					
Charlson comorbidity points	6.43 (2.82)	6.47 (3.0)	6.41 (2.72)	1.008 (0.992 to 1.024)	.3251
Depression	1719 (20.4)	711 (24.2)	1,008 (18.3)	1.422 (1.369 to 1.478)	< .0001

Abbreviation: OR, odds ratio.

TABLE 2. Key Features of the Primary Model

Variable Name	β	OR (95% CI)	*P*	Variable Type
Prior hospitalizations (No.)	0.30	1.35 (1.20 to 1.51)	8.2E–07	Utilization
Depression	0.29	1.33 (1.13 to 1.56)	4.5E–04	Diagnoses
Alkaline phosphatase level	0.19	1.20 (1.09 to 1.34)	4.4E–04	Labs
Stage IV disease	0.17	1.19 (1.06 to 1.33)	3.1E–03	Cancer-specific
Lipase level	0.16	1.17 (1.06 to 1.29)	1.7E–03	Procedures
Oxygen saturation	0.11	1.12 (1.01 to 1.24)	3.8E–02	Labs
Pulse	0.09	1.09 (1.02 to 1.17)	1.1E–02	Vitals
Brainstem MRI	0.08	1.08 (1.00 to 1.17)	4.4E–02	Procedures
Cancer antigen 19-9 level	0.08	1.08 (1.02 to 1.14)	1.2E–02	Labs
Vitamin B12 level	–0.07	0.93 (0.87 to 1.00)	4.2E–02	Labs
C-reactive protein level	–0.08	0.92 (0.86 to 0.99)	1.9E–02	Labs
Lipase level	–0.09	0.91 (0.85 to 0.98)	7.2E–03	Labs
White race	–0.12	0.89 (0.82 to 0.97)	5.2E–03	Demographics
White blood cell count	–0.26	0.77 (0.67 to 0.90)	5.5E–04	Labs
Electrolyte maintenance medications	–0.34	0.71 (0.58 to 0.87)	9.0E–04	Medication

Abbreviations: MRI, magnetic resonance imaging; OR, odds ratio.

to be at the 64th percentile of risk or higher, and these patients had significantly higher predicted risk percentiles than those with private insurance (61.97 ± 26.20 *v* 51.65 ± 29.38, *P* = .002). When examining the interaction between race and insurance type, there was an additive effect between being Black and having Medicaid insurance (Fig 3D).

Effect of PROs on Model Performance

Finally, to evaluate the impact PROs have on predictive performance, new LASSO models were trained to predict the risk for OP-35 events at 180 days on the subset of patients who had PRO data (n = 1,808). The baseline model on this data set performed with an AUROC of 0.735 (95% CI, 0.673 to 0.799). With the inclusion of PRO data, performance did

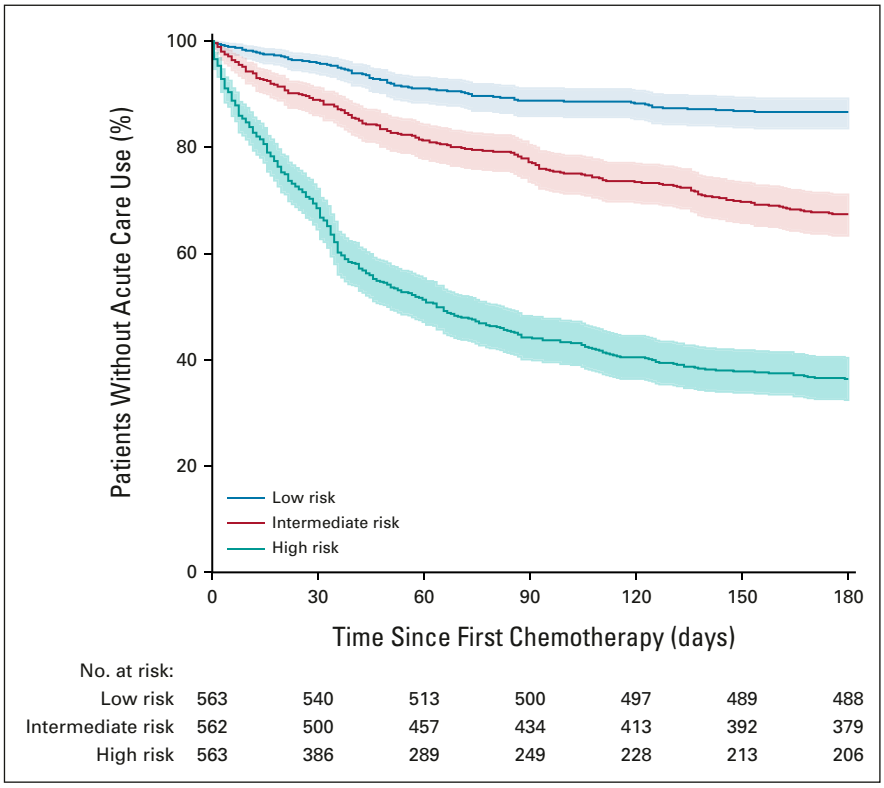

FIG 2. Risk-stratified Kaplan-Meier survival curves for ACU. Kaplan-Meier curves for preventable ACU events for patients in the test cohort stratified by predicted risk tertile. Shaded area represents 95% CIs. ACU, acute care use.

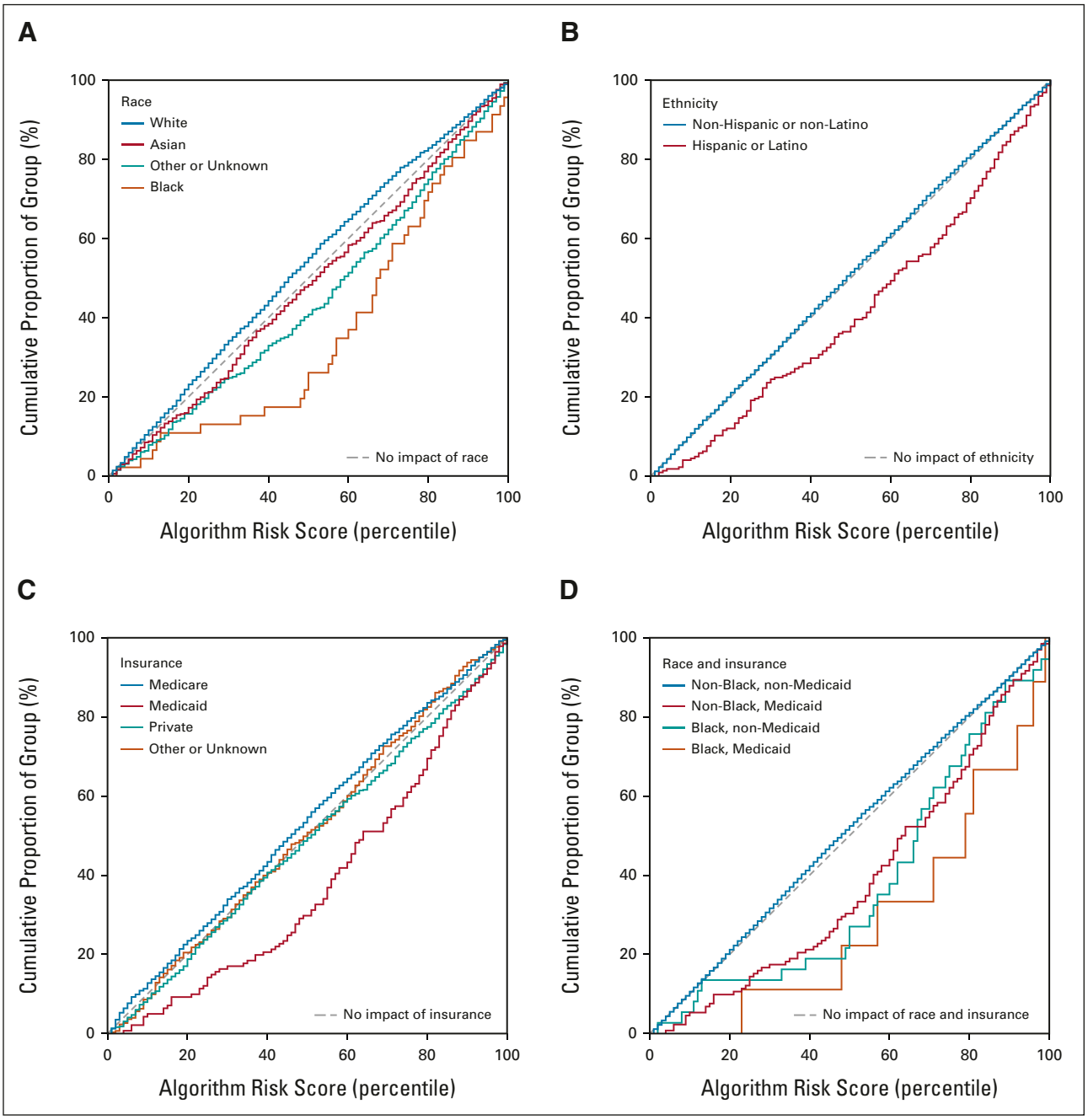

FIG 3. Algorithmic risk scores stratified by race, ethnicity, and insurance status. Empiric cumulative distribution plots for the percentile of predicted risk for the test cohort stratified by (A) race, (B) ethnicity, (C) insurance status, and (D) the interaction between Black race and Medicaid.

not significantly change (AUROC 0.736; 95% CI, 0.673 to 0.798), but the model required only 41 features for comparable performance as compared to the 125 in the original model. PROMIS features selected by the model included the global physical health score, the self-reported pain score, and the self-reported quality of life score.

DISCUSSION

Improving the care and outcomes of patients with cancer undergoing chemotherapy must incorporate insights learned from AI-driven decision support. In this study, we identify patients at high risk for preventable acute care, the target of CMS's OP-35 measure, using ML models trained on routinely collected clinical data that demonstrated strong predictive performance. Our primary model was able to accurately discriminate patients at high risk for ACU versus low risk at an actionable level of accuracy. As payment models move to incorporate more value-based care measures and regulatory agencies demand the incorporation of real-world data to guide clinical practice, the

open-source, ML-based tool we present has strong clinical utility and the potential to improve the identification and mitigation of these high-risk patients.

Our work presents a model focused specifically on OP-35 eligible admissions and ED visits, which can be implemented by health care systems that routinely capture prechemotherapy data on their patients by following our methodology. The regression coefficients that were selected by the LASSO model are generally consistent with previously reported literature about risk factors for ACU for patients with cancer; for example, previous ED admissions,[25] neutropenia,[26] and depression[27] have all been shown to be associated with unplanned admissions in previous studies. In addition, the model selected novel features not typically included in risk models, such as depression and prior brain imaging, indicating that there is likely loss of predictive information when using a small subset of clinical variables. The limited declines in predictive performance when withholding entire feature categories from the model further suggest that missing predictive information can be partially recovered from other parts of the patient record and there are likely many plausible explanatory models when using dense data. Compared to previous work predicting ACU in patients with cancer, we used OP-35 inclusion criteria to identify preventable ACU, limited data input to only include data up to the initiation of chemotherapy, and took advantage of the richness of data offered by the EHR, incorporating more information about the patient's overall health to aid with prediction by using more than 750 EHR-derived features, whereas prior studies have made use of a much smaller set of clinical features.[14,15,28,29]

The very modest gains in predictive performance when including PROs expands upon recent work integrating PROs in ML models. Seow et al[30] developed an ML model to predict cancer patient survival that integrated clinical characteristics and PROs to achieve strong predictive performance and calibration; however, it is unclear what benefit PRO inclusion provided to their predictions, as they do not report a model when withholding PROs.[30] Although PROs are a critical component of evaluating modern oncology care, similar to our study, Grant et al recently showed that PROs did not improve performance when predicting ACU, suggesting their use may be somewhat limited in this particular prediction task.[14,31] Importantly, this study shows that PROs provide some predictive power to determine risk for ACU, but they do not substantially add to model performance when sufficient structured EHR data are available for predictions.

Given the prior evidence of inequitable outcomes on the basis of demographic subgroup and insurer, we felt it was important to provide race, ethnicity, and insurance data to our models to study their respective effects.[32-36] Our results further indicate that Black race and Medicaid payor are predictive of increased risk for ACU. In particular, our findings that patients with cancer with Medicaid insurance have higher risk scores for ACU are aligned with previous findings and suggest that Medicaid is correlated with poor patient outcomes. Although our analyses are not designed to address causation, our results support further study of these discrepancies for evaluation and the identification of methods to mitigate identified inequalities. Our health care system strives to equalize resource allocation; however, these results suggest that Medicaid and Black patients need closer monitoring than others to achieve equitable outcomes. This phenomenon is not localized to our health care system, as others have shown similar results across diverse settings.[37] There is a growing shift in care delivery that emphasizes equitable outcomes over equal access to resources. A potential strategy to address this lack of equitable outcomes would be to ensure Medicaid and Black patients undergoing chemotherapy have more frequent follow-up and closer monitoring of symptoms than non-Hispanic Whites and patients insured by Medicare or private companies. Such strategies could potentially help decrease unethical gaps in outcomes. Additionally, the poor calibration of our models for certain demographic groups highlights the critical importance of making clinicians aware of potential biases in risk models when using these to make care decisions to limit perpetuation of bias and exacerbation of inequities.

Clinical implementation of this model can help provide outpatient physicians a data-driven tool to identify patients who are at highest risk of unplanned ED or IP admission and preemptively intervene. We envision a sliding scale of interventions on the basis of the risk cohort that the patient falls into, determined by their ML risk score.[38] For example, high-risk patients could be prioritized for advanced home-based health care,[39] frequent nursing follow-up phone calls to manage outpatient symptoms and answer questions,[40] or home telemonitoring services.[41] Targeting these interventions to high-risk cohorts is a cost-effective way for health care systems to manage large populations of oncology patients in a data-driven manner and is already being implemented in some health systems. A recent report that prospectively validated a similar ACU prediction model in radiotherapy patients demonstrated a 10% reduction in ACU for patients who received more frequent evaluation after being identified by an algorithm as high risk.[29,42] From the patient's perspective, ML-guided interventions to reduce ACU would be beneficial, as increasing the number of days at home during chemotherapy and end-of-life oncology care is an important metric for quality of life.[43]

There are several limitations that are important to consider in this study. First, this study was performed at a large, academic medical center with multiple specialty oncology practices. In particular, the small number of Black and Black Medicaid patients in our analytic cohort, which reflects the current catchment area of our institution, may limit the generalizability of our analysis. Our cancer center is

expanding its catchment area to include treatment centers serving more currently under-represented minorities in our common EHR information platform, which we will use to confirm our analyses and test interventions. External validation of this model at both academic and nonacademic hospitals is needed to ensure generalizability; however, this may prove difficult because of variations in EHR implementations resulting in nonparsimonious models. We plan to develop models on the basis of a common data model, readily allowing for exportation to other systems. In the interim, we encourage other health systems to follow our methodology and expand upon our results. Second, our model relies upon a large number of clinical variables, and although many of these values are routinely collected in the EHR, developing an information technology pipeline that reliably and accurately retrieves these data from the EHR for real-time predictions at the point of care could prove challenging. Third, our model is focused on a binary prediction of ACU within specific follow-up windows; however, there are many patients who will often have repeat admissions within the same follow-up window, significantly driving up utilization and costs.[26] Future prediction models could be used to identify the number of ACU events per patient within prediction windows, giving health care systems more granular data to determine which patients would most likely benefit from preventative admission interventions. Fourth, our utilization and mortality data are limited to ED visits and admissions in our health care system and deaths captured by our cancer registry. Therefore, the data may be missing deaths and acute care services rendered elsewhere. Finally, although we developed a model for all patients receiving chemotherapy, regardless of the underlying cancer etiology, it is likely that models for specific cancer types would have improved performance at the expense of generalizability.

In conclusion, in this study, we present a data-driven model to identify chemotherapy patients at high risk for preventable ACU, as defined by CMS's OP-35 quality measure. We found that an ML model trained on a large number of routinely collected clinical variables can accurately identify patients at risk for ACU while on chemotherapy before starting treatment. Our model selected clinical features used in prior risk models and other less commonly used features to produce predictions with an actionable level of accuracy. Additionally, the inherent bias in our models and data demonstrate inequity in both health care systems and risk models and suggest Medicaid and Black patients would benefit from closer monitoring than others to achieve equitable outcomes. Further work will be needed to validate our models in other health care systems and assess the clinical impact of pretreatment risk predictions. Nonetheless, ML models can risk-stratify patients, allowing for differential intensity of monitoring and targeted, preventative interventions, and have potential to improve cancer care outcomes, costs, and patient experience.

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DISCLAIMER

The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

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DATA SHARING STATEMENT

The analysis code for this study is available at https://github.com/dylan-peterson-95/predicting-preventable-admissions. As we are unable to share PHI, there are simulated data available in the repository with an example of how to generate model predictions.

AUTHOR CONTRIBUTIONS

Conception and design: All authors
Financial support: Tina Hernandez-Boussard
Administrative support: James D. Brooks, Tina Hernandez-Boussard
Provision of study materials or patients: Tina Hernandez-Boussard
Collection and assembly of data: Dylan J. Peterson
Data analysis and interpretation: All authors
Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated unless otherwise noted. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/cci/author-center.

Open Payments is a public database containing information reported by companies about payments made to US-licensed physicians (Open Payments).

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Consulting or Advisory Role: Creare, Daiichi Sankyo, Embold Health, Lilly, Google, G1 Therapeutics, Merck, BMS, Incyte

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APPENDIX 1

Data Preprocessing

Vital sign data were first cleaned of values incompatible with life as determined by clinician input. Next, a time-weighted average of vital sign data was calculated for each patient, with values close to the first date of chemotherapy more heavily weighted while still accounting for historical trends. This was done using the formula $f_{i,j} = \frac{\sum_{t=1}^{n} f_{i,j,t} e^{-t/180}}{\sum_{t=1}^{n} e^{-t/180}}$, where i indicates the feature, j indicates the participant, and t is the number of days before the start of chemotherapy for that participant. Missing vitals were then mean imputed if not present. Similarly, a time-weighted count for each procedure code was generated for each patient, with more recent procedures receiving higher values using the above formula. Individual medications were mapped to pharmacologic classes, and patients were given binary values for prescribed or not in the 180 days before chemotherapy. Health care utilization features included the number of prechemotherapy emergency department, inpatient, and psychiatry department visits, the proportion of emergency department visits that resulted in admission, and the average length of inpatient stays. For laboratory data, each laboratory was harmonized to common units, and then, a time-weighted average for each laboratory feature was calculated using the above formula. K Nearest Neighbors (KNN) imputation was then used to fill missing values with patients receiving the mean value of the 10 patients in the training set with the most similar laboratory profile on the basis of the laboratory data they did have. The KNN-imputer fit on the training set was used to impute missing values for both the training and testing cohorts. Additional features engineered included the total number of procedures, diagnoses, and medications that a patient had. To limit sparsity in the data, as most procedures, medications, diagnoses, and labs were only present in a limited subset of the cohort, features in these categories present in $< 2.5\%$ of the training cohort were excluded, yielding a total of 759 features. To complete preprocessing, each of the continuous variables was scaled to a standard normal distribution.

Models Trained

A total of nine models were trained. These included least absolute shrinkage and selection operator (LASSO), Ridge, and elastic net penalties, random forests, gradient-boosted model (GBM) trees, multilayer perceptron neural networks, support vector machines, KNN classifiers, and ensemble voting models that used equal voting on the predictions from the LASSO, ridge, elastic net, random forest, GBM, and support vector machines for a given outcome. A grid search with 10-fold cross-validation was used to tune hyperparameters and optimize performance on the training cohort using the area under the receiver operator curve metric (see Appendix Table A1 for the hyperparameter tuning details for each model). Except for the LASSO model, the best performing model from the grid search was then selected for evaluation for each outcome-model pair. For the LASSO model, we selected the most regularized model with a cross-validated error within 1 standard error of the minimum during cross validation (ie, the model using a lambda equal to the lambda.1se parameter returned from the cv.glmnet function).

Analysis Code

All codes were written in Python 3.6 (Python Software Foundation, https://www.python.org/), and all models were implemented using the scikit-learn package (version 0.22.1) with the exception of the GBM models, which were implemented using LightGBM (version 2.3.1), and the LASSO models, which were implemented in R 4.0.2 (The R Project for Statistical Computing, https://www.r-project.org/) using the glmnet package (version 4.1) with feature CIs generated by the selectiveInference package (version 1.2.5; Pedregosa F, et al: Scikit-learn: Machine Learning in Python; Ke G, et al: Curran Associates, 2017, pp 3149-3157; Friedman JH, et al: J Stat Softw 33:1-22, 2010; Tibshirani R, et al: 2019. https://CRAN.R-project.org/package=selectiveInference).

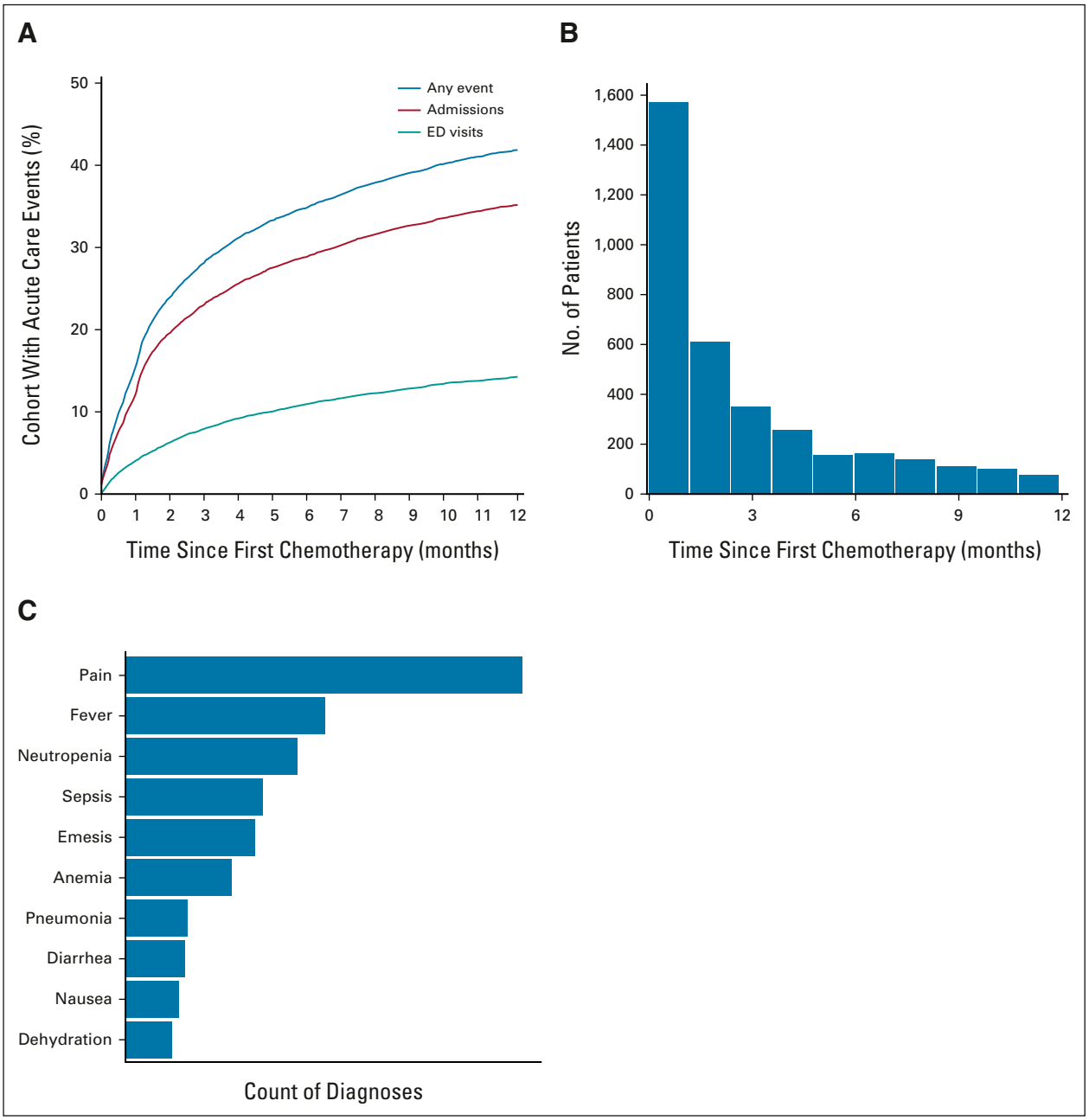

FIG A1. OP-35 events in cohort. (A) Cumulative proportion of the cohort with an OP-35 event after time chemotherapy imitation. (B) Distribution of time from chemotherapy initiation to first OP-35 event in the cohort. (C) Distribution of diagnoses associated with the first OP-35 event for patients in the cohort. ACU, acute care use; ED, emergency department.

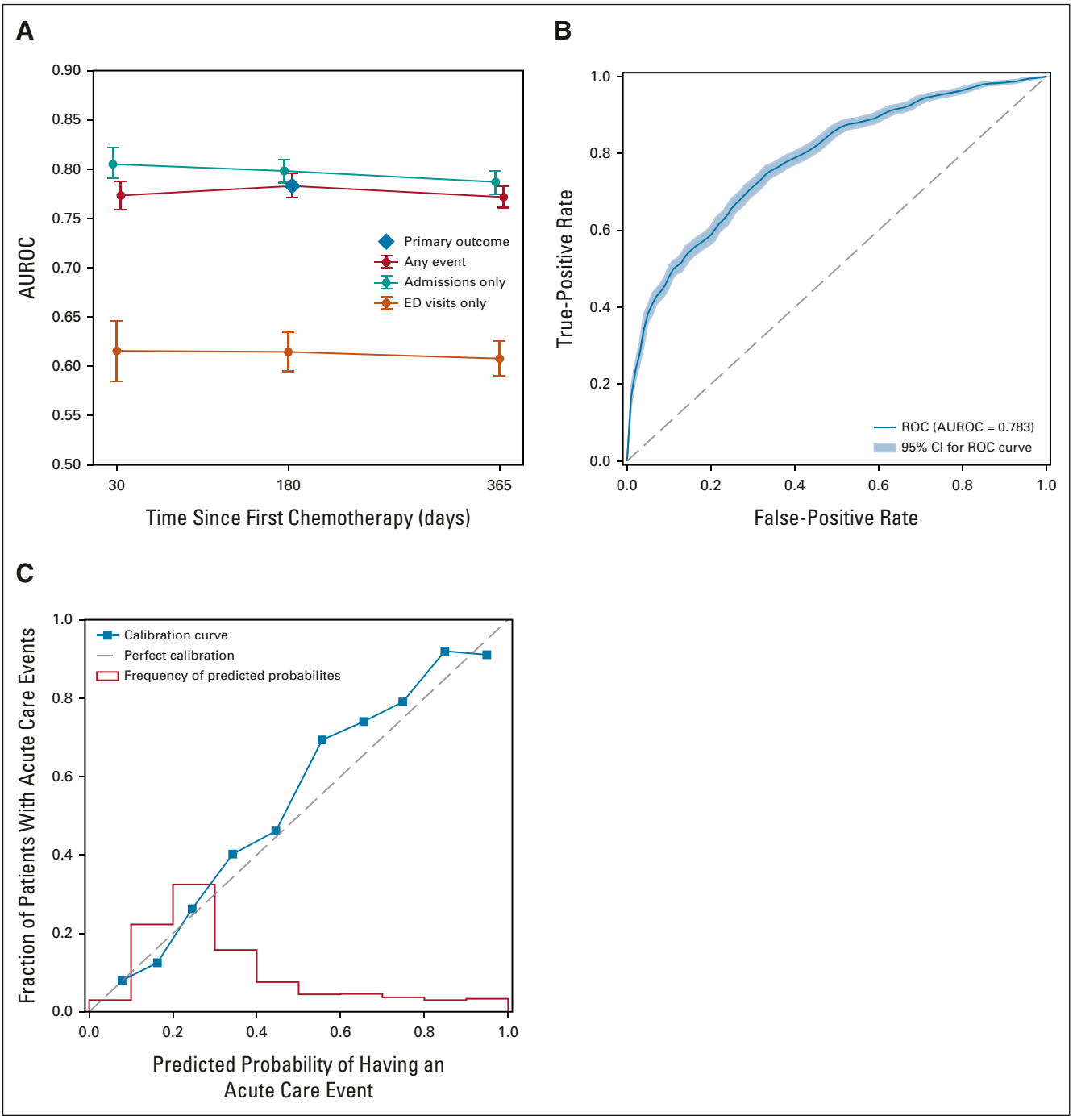

FIG A2. LASSO Model Performance. (A) Performance of primary LASSO model for predicting any OP-35 event, admissions-only OP-35 events, and ED visits-only OP-35 events at 30, 180, and 365 days. Vertical bars indicate 95% CIs. (B) ROC for the LASSO model when predicting any OP-35 event at 180 days. Shaded area indicates 95% CI. (C) Calibration curve for the LASSO model when predicting any OP-35 event at 180 days (blue) and distribution of predicted probabilities of having an OP-35 event by 180 days (red). AUROC, area under the receiver operator curve; ED, emergency department; LASSO, least absolute shrinkage and selection operator; ROC, receiver operator curve.

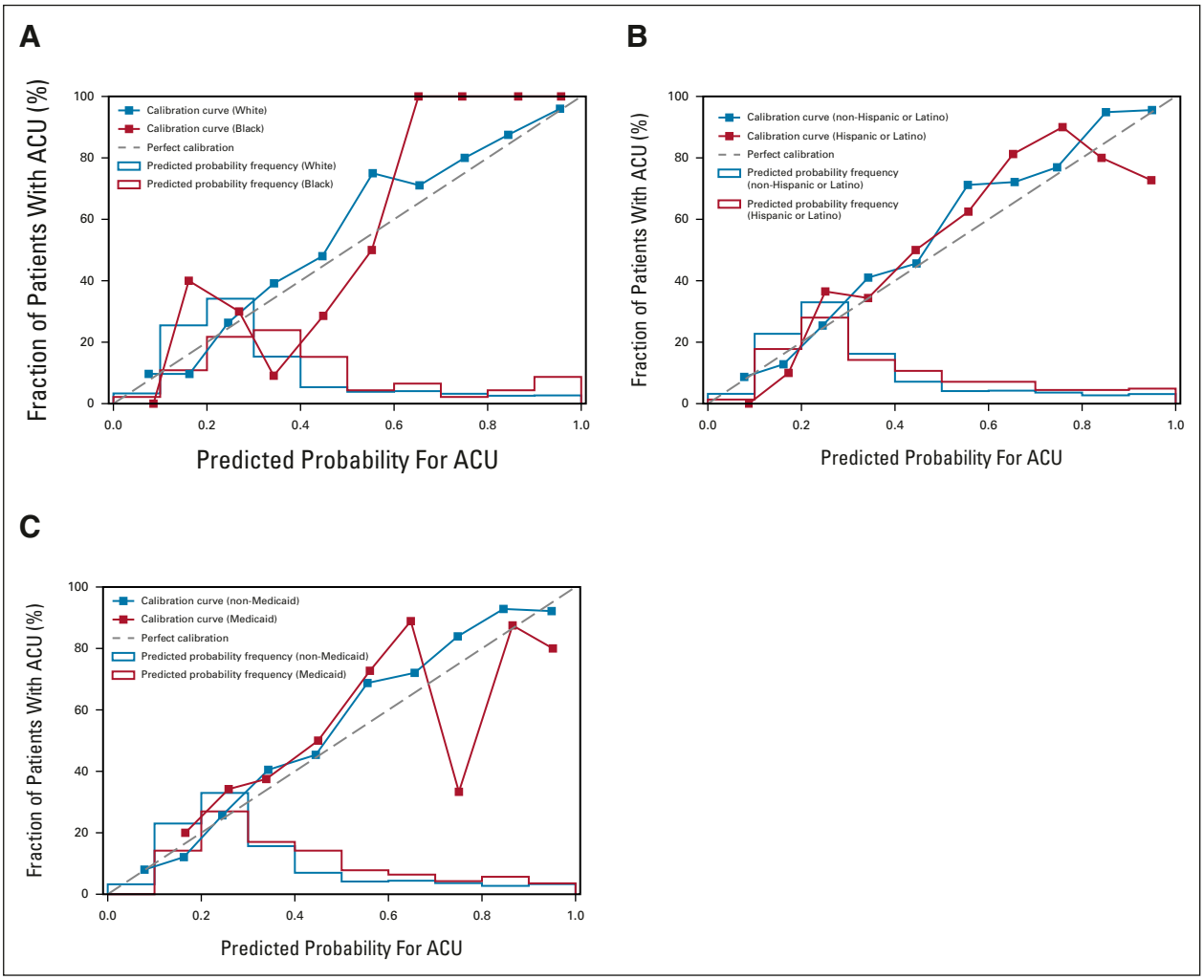

FIG A3. LASSO model calibration for demographic subgroups. Calibration curves and histograms of predicted probabilities for ACU for the primary LASSO model, stratified by demographic subgroups: (A) White versus Black patients, (B) Hispanic or Latino versus non-Hispanic or non-Latino patients, and (C) Medicaid versus non-Medicaid patients. ACU, acute care use; LASSO, least absolute shrinkage and selection operator.

TABLE A1. Hyperparameter Tuning

Model	Hyperparameter	Values Searched
LASSO	lambda	Default parameters for cv.glmnet. For primary model: 94 values from 1.24×10^{-1} to 2.17×10^{-5}
Ridge	C	10^{-8}, 10^{-7}, 10^{-6}, 10^{-5}, 10^{-4}, 10^{-3}, 10^{-2}, 10^{-1}, 1, 10^{1}, 10^{2}
ELNET	C l1_ratio	10^{-8}, 10^{-7}, 10^{-6}, 10^{-5}, 10^{-4}, 10^{-3}, 10^{-2}, 10^{-1}, 1, 10^{1}, 10^{2} 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9
RF	min_sample_split max_features	2, 5, 10, 100 auto, none
GBM	learning_rate num_leaves	0.01, 0.05, 0.1, 0.5 10, 25, 100
SVM	C kernel	10^{-4}, 10^{-3}, 10^{-2}, 10^{-1}, 1, 10^{1}, 10^{2}, 10^{3}, 10^{4} linear, poly, rbf, sigmoid
KNN	N_neighbors weights	1, 2, 3, 4, 5, 6, 7, 8, 9, 10 uniform, distance
MLP	alpha hidden_layer_size	10^{-4}, 10^{-3}, 10^{-2}, 10^{-1}, 1, 10^{1}, 10^{2}, 10^{3}, 10^{4} (100, 50, 10), (100, 162, 10), (100, 275, 10), (100, 387, 10), (100, 500, 10), (325, 50, 10), (325, 162, 10), (325, 275, 10), (325, 387, 10), (325, 500, 10), (550, 50, 10), (550, 162, 10), (550, 275, 10), (550, 387, 10), (550, 500, 10), (775, 50, 10), (775, 162, 10), (775, 275, 10), (775, 387, 10), (775, 500, 10), (1,000, 50, 10), (1,000, 162, 10), (1,000, 275, 10), (1,000, 387, 10), (1,000, 500, 10)

NOTE. Hyperparameter names are defined in Scikit-learn 0.22.1 and glmnet.

Abbreviations: ELNET, elastic net; GBM, gradient-boosted model; KNN, K Nearest Neighbor; LASSO, least absolute shrinkage and selection operator; MLP, multilayered perceptron; RF, random forest; SVM, support vector machine.

TABLE A2. Model AUROCs

Outcome	Time	Model	AUROC	AUROC 95% CI
ANY	30	elnet	0.8020	0.7885 to 0.8165
ANY	30	ffnn	0.7937	0.7795 to 0.8080
ANY	30	gbm	0.7940	0.7776 to 0.8105
ANY	30	knn	0.6905	0.6738 to 0.7078
ANY	30	lasso	0.7807	0.7652 to 0.7960
ANY	30	lasso_180d	0.7737	0.7597 to 0.7882
ANY	30	Rf	0.7958	0.7815 to 0.8091
ANY	30	ridge	0.8010	0.7876 to 0.8147
ANY	30	svm	0.7887	0.7745 to 0.8045
ANY	30	voting	0.8115	0.7977 to 0.8256
ANY	180	elnet	0.7939	0.7826 to 0.8049
ANY	180	ffnn	0.7993	0.7880 to 0.8100
ANY	180	gbm	0.8013	0.7903 to 0.8122
ANY	180	knn	0.7403	0.7276 to 0.7534
ANY	180	lasso	0.7813	0.7696 to 0.7930
ANY	180	lasso_180d	0.7833	0.7728 to 0.7953
ANY	180	Rf	0.7878	0.7767 to 0.7994
ANY	180	ridge	0.7967	0.7857 to 0.8072
ANY	180	svm	0.7840	0.7724 to 0.7944
ANY	180	voting	0.8057	0.7948 to 0.8162
ANY	365	elnet	0.7887	0.7780 to 0.8000
ANY	365	ffnn	0.7904	0.7795 to 0.8012
ANY	365	gbm	0.7971	0.7866 to 0.8079
ANY	365	knn	0.7211	0.7086 to 0.7342
ANY	365	lasso	0.7837	0.7725 to 0.7938
ANY	365	lasso_180d	0.7721	0.7607 to 0.7837
ANY	365	Rf	0.7834	0.7727 to 0.7949
ANY	365	ridge	0.7941	0.7837 to 0.8047
ANY	365	svm	0.7884	0.7780 to 0.7998
ANY	365	voting	0.8021	0.7919 to 0.8131
ED	30	elnet	0.6395	0.6060 to 0.6715
ED	30	ffnn	0.6532	0.6265 to 0.6813
ED	30	gbm	0.6165	0.5808 to 0.6581
ED	30	knn	0.5001	0.4755 to 0.5202
ED	30	lasso	0.6086	0.5788 to 0.6385
ED	30	lasso_180d	0.6159	0.5873 to 0.6479
ED	30	Rf	0.6284	0.5981 to 0.6609
ED	30	ridge	0.6417	0.6129 to 0.6705
ED	30	svm	0.5740	0.5422 to 0.6082
ED	30	voting	0.6290	0.5955 to 0.6614
ED	180	elnet	0.6910	0.6732 to 0.7105
ED	180	ffnn	0.6581	0.6381 to 0.6786
ED	180	gbm	0.6639	0.6428 to 0.6840
ED	180	knn	0.5600	0.5383 to 0.5783
ED	180	lasso	0.6651	0.6454 to 0.6845
ED	180	lasso_180d	0.6149	0.5952 to 0.6353
ED	180	Rf	0.6317	0.6115 to 0.6517
ED	180	ridge	0.6730	0.6539 to 0.6920
ED	180	svm	0.6143	0.5933 to 0.6355
ED	180	voting	0.6658	0.6465 to 0.6848
ED	365	elnet	0.6763	0.6592 to 0.6945
ED	365	ffnn	0.6743	0.6569 to 0.6923
ED	365	gbm	0.6619	0.6426 to 0.6807
ED	365	knn	0.5666	0.5484 to 0.5848
ED	365	lasso	0.6800	0.6635 to 0.6975
ED	365	lasso_180d	0.6084	0.5895 to 0.6259
ED	365	Rf	0.6449	0.6266 to 0.6633
ED	365	ridge	0.6786	0.6608 to 0.6956
ED	365	svm	0.6422	0.6249 to 0.6628
ED	365	voting	0.6784	0.6610 to 0.6959
HOSP	30	elnet	0.8328	0.8192 to 0.8475
HOSP	30	ffnn	0.8304	0.8158 to 0.8457
HOSP	30	gbm	0.8340	0.8188 to 0.8505
HOSP	30	knn	0.7240	0.7053 to 0.7414
HOSP	30	lasso	0.8039	0.7869 to 0.8216
HOSP	30	lasso_180d	0.8056	0.7907 to 0.8212
HOSP	30	Rf	0.8300	0.8162 to 0.8453
HOSP	30	ridge	0.8339	0.8202 to 0.8484
HOSP	30	svm	0.8207	0.8054 to 0.8354
HOSP	30	voting	0.8451	0.8321 to 0.8590
HOSP	180	elnet	0.8056	0.7947 to 0.8173
HOSP	180	ffnn	0.8011	0.7895 to 0.8126
HOSP	180	gbm	0.8152	0.8044 to 0.8270
HOSP	180	knn	0.7534	0.7402 to 0.7678
HOSP	180	lasso	0.7930	0.7822 to 0.8053
HOSP	180	lasso_180d	0.7983	0.7867 to 0.8093
HOSP	180	Rf	0.8044	0.7919 to 0.8166
HOSP	180	ridge	0.8069	0.7962 to 0.8175
HOSP	180	svm	0.7994	0.7878 to 0.8105
HOSP	180	voting	0.8181	0.8075 to 0.8291
HOSP	365	elnet	0.7999	0.7895 to 0.8111
HOSP	365	ffnn	0.8041	0.7926 to 0.8149
HOSP	365	gbm	0.8065	0.7957 to 0.8178
HOSP	365	knn	0.7436	0.7314 to 0.7563
HOSP	365	lasso	0.7879	0.7760 to 0.7992
HOSP	365	lasso_180d	0.7870	0.7765 to 0.7980
HOSP	365	Rf	0.7944	0.7837 to 0.8053
HOSP	365	ridge	0.8003	0.7902 to 0.8124
HOSP	365	svm	0.8000	0.7896 to 0.8120
HOSP	365	voting	0.8108	0.8003 to 0.8215

Abbreviations: ANY, any OP-35 event; AUROC, area under the receiver operator curve; ED, emergency department visit-only OP-35 events; elnet, elastic net; gbm, gradient-boosted trees; ffnn, multilayer perceptron neural networks; HOSP, admission-only OP-35 events; knn, K Nearest Neighbors; lasso, least absolute shrinkage and selection operator; lasso_180d, performance of LASSO trained for predicting at 180 days at alternative outcomes; rf, random forests; svm, support vector machines; voting, ensemble voting.

TABLE A3. All Least Absolute Shrinkage and Selection Operator Coefficients

Feature Name	Beta	OR	95% CI	*P*	Feature Type
HOSP_N	0.2969	1.3457	1.1959 to 1.5144	8.21E–07	UTIL
ALKP	0.1857	1.2041	1.0857 to 1.3353	4.36E–04	LABS
DEPRESSED	0.2863	1.3314	1.1347 to 1.5622	4.48E–04	DEMO
WBC	–0.2551	0.7748	0.6704 to 0.8955	5.50E–04	LABS
ELECTROLYTE MAINTENANCE	–0.3414	0.7108	0.5810 to 0.8695	9.03E–04	RX
CEA	–0.0918	0.9123	0.8634 to 0.9640	1.09E–03	LABS
ENCOUNTER FOR ANTINEOPLASTIC CHEMOTHERAPY	0.3495	1.4183	1.1437 to 1.7589	1.46E–03	DX
LIPASE	0.1582	1.1714	1.0611 to 1.2931	1.72E–03	PROC
UNLIS MISC DX NUC MED	0.1029	1.1084	1.0381 to 1.1834	2.07E–03	PROC
STAGE_4	0.1712	1.1868	1.0596 to 1.3292	3.07E–03	DEMO
WHITE	–0.1174	0.8893	0.8189 to 0.9656	5.24E–03	DEMO
LIPASE	–0.0926	0.9115	0.8520 to 0.9752	7.16E–03	LABS
CYANOCOBALAMIN	0.0860	1.0898	1.0236 to 1.1603	7.18E–03	PROC
PULSE	0.0893	1.0934	1.0204 to 1.1716	1.13E–02	VITALS
C199	0.0758	1.0787	1.0166 to 1.1446	1.22E–02	LABS
CRP	–0.0822	0.9211	0.8597 to 0.9868	1.94E–02	LABS
ANTB PROTOZOA NES	0.5443	1.7234	1.0903 to 2.7239	1.98E–02	PROC
IA TUM AG QUAN CA 19-9	0.0942	1.0987	1.0123 to 1.1926	2.43E–02	PROC
INSJ PRPH CVC W/O SUBQ PORT/PMP AGE 5 YR/>	0.0830	1.0866	1.0106 to 1.1682	2.47E–02	PROC
IMMUNOHISTO ANTIBODY STAIN	0.1101	1.1164	1.0130 to 1.2304	2.63E–02	PROC
O2SATV	0.1121	1.1186	1.0062 to 1.2436	3.80E–02	LABS
B12	-0.0680	0.9342	0.8749 to 0.9975	4.20E–02	LABS
MRI BRN BRN STEM C–/C+	0.0792	1.0824	1.0021 to 1.1693	4.41E–02	PROC
M/PHMTRC ALYS ISH EA PRB MNL	0.0795	1.0827	1.0010 to 1.1712	4.73E–02	PROC
PTT	–0.0697	0.9326	0.8697 to 1.0001	5.04E–02	LABS
CUL BACT QUAN COLONY CNT URINE	0.0866	1.0904	0.9998 to 1.1892	5.04E–02	PROC
LVL VI-SURG PATH GROSS & MCRSCP XM	–0.0781	0.9249	0.8551 to 1.0003	5.10E–02	PROC
METHB	–0.0571	0.9445	0.8911 to 1.0011	5.46E–02	LABS
LYM	–0.1465	0.8637	0.7419 to 1.0055	5.89E–02	LABS
SEDIMENTATION RATE RBC AUTO	–0.0656	0.9365	0.8748 to 1.0025	5.90E–02	PROC
TSH	0.0559	1.0575	0.9978 to 1.1208	5.93E–02	LABS
ED VISIT—HIGH SEVERITY NON LIFE THREAT—LEVEL 4	0.1002	1.1054	0.9955 to 1.2274	6.08E–02	PROC
BLD SMR PRPH INTERPJ PHYS WRTTN REPRT	0.0816	1.0850	0.9955 to 1.1825	6.32E–02	PROC
DUPLEX VESSEL FLOW STUDY	0.0667	1.0690	0.9960 to 1.1473	6.44E–02	PROC
GG IGA IGD IGG IGM EA	–0.0588	0.9429	0.8856 to 1.0040	6.63E–02	PROC
CL	–0.0622	0.9397	0.8785 to 1.0052	7.02E–02	LABS
THER PROPH/DX NJX IV PUSH SINGLE/1ST SBST/DRUG	0.0857	1.0895	0.9916 to 1.1970	7.42E–02	PROC
LDH	0.0713	1.0739	0.9923 to 1.1622	7.70E–02	LABS
PRST8 SPEC AG TOT	–0.0897	0.9142	0.8262 to 1.0114	8.19E–02	PROC
DDIMER	–0.0595	0.9423	0.8804 to 1.0084	8.59E–02	LABS
SYPHILIS TST QUAL	0.1855	1.2038	0.9707 to 1.4929	9.12E–02	PROC
ANTB HERPES SMPLX TYP 1	–0.2639	0.7680	0.5572 to 1.0586	1.07E–01	PROC
CHEMOTX ADMN SUBQ/IM HORMONAL ANTI-NEO	–0.2839	0.7529	0.5326 to 1.0642	1.08E–01	PROC
INSJ TUN CTR CTR VAD W/SUBQ PORT AGE 5 YR/>	0.1965	1.2171	0.9568 to 1.5483	1.10E–01	PROC

(continued on following page)

TABLE A3. All Least Absolute Shrinkage and Selection Operator Coefficients (continued)

Feature Name	Beta	OR	95% CI	*P*	Feature Type
ANTB HERPES SMPLX TYP 2	–0.2205	0.8021	0.6122 to 1.0510	1.10E–01	PROC
ANES UPPER GI ENDOSCOPIC PROXIMAL TO DUODENUM	0.0599	1.0618	0.9866 to 1.1427	1.10E–01	PROC
LDLHDL	–0.0694	0.9330	0.8549 to 1.0181	1.19E–01	LABS
TOTALCELLCNT	0.0462	1.0473	0.9880 to 1.1102	1.20E–01	LABS
PSA	–0.0517	0.9497	0.8895 to 1.0139	1.22E–01	LABS
CALCIUM TOT	–0.0936	0.9106	0.8065 to 1.0281	1.30E–01	PROC
MRI SPI CANAL & CNTS C–/C+	0.0690	1.0714	0.9788 to 1.1728	1.35E–01	PROC
LYMPH	–0.0595	0.9422	0.8712 to 1.0189	1.36E–01	LABS
EVAL/MGMT OF NEW PATIENT—LEVEL 4	0.0444	1.0454	0.9859 to 1.1086	1.37E–01	PROC
BAND	–0.0527	0.9486	0.8841 to 1.0178	1.42E–01	LABS
ALT	–0.0702	0.9322	0.8432 to 1.0306	1.70E–01	LABS
TROPONIN QUAN	0.0593	1.0611	0.9730 to 1.1572	1.80E–01	PROC
RBC	–0.2486	0.7799	0.5420 to 1.1220	1.80E–01	LABS
LVEF	–0.0390	0.9617	0.9083 to 1.0183	1.81E–01	LABS
DESIGN MLC DEVICE FOR IMRT	–0.1954	0.8225	0.6171 to 1.0964	1.83E–01	PROC
CARCINOEMBRYONIC AG	0.0517	1.0530	0.9750 to 1.1373	1.88E–01	PROC
GONAD CHORNC QUAL	0.0391	1.0399	0.9806 to 1.1027	1.92E–01	PROC
NTSTY MODUL RAD TX DLVR CPLX	–0.0541	0.9474	0.8722 to 1.0289	1.99E–01	PROC
COMPRHNSV HX/EXAM INIT HOSPITAL MOD SEV 50 MIN	0.0489	1.0501	0.9720 to 1.1346	2.15E–01	PROC
EVAL/MGMT OF NEW PATIENT—LEVEL 5	0.0403	1.0411	0.9764 to 1.1102	2.18E–01	PROC
UPH	0.0367	1.0374	0.9783 to 1.1000	2.20E–01	LABS
ALB	–0.1559	0.8556	0.6656 to 1.0998	2.24E–01	LABS
LYMPHATICS & LYMPH NOD IMG	–0.0600	0.9418	0.8542 to 1.0384	2.29E–01	PROC
FERRITIN	–0.0861	0.9175	0.7963 to 1.0571	2.34E–01	PROC
MCHC	–0.1285	0.8794	0.7066 to 1.0946	2.50E–01	LABS
FLUOR GID CTR VAD PLMT RPLCMT/RMVL	–0.1512	0.8597	0.6640 to 1.1130	2.51E–01	PROC
BUN	0.0490	1.0502	0.9652 to 1.1427	2.56E–01	LABS
NAN	–0.0790	0.9241	0.8054 to 1.0602	2.60E–01	DX
GLU	0.0503	1.0515	0.9611 to 1.1505	2.73E–01	LABS
PSYCH_N	0.0303	1.0308	0.9763 to 1.0884	2.74E–01	UTIL
AGE_AT_CHE	0.8353	2.3055	0.5091 to 10.4416	2.78E–01	DEMO
EVAL/MGMT OF EST PATIENT	–0.0372	0.9634	0.8985 to 1.0330	2.95E–01	PROC
MRI ORBIT FACE & NCK C–/C+	0.0354	1.0361	0.9685 to 1.1083	3.03E–01	PROC
AG	0.0415	1.0424	0.9630 to 1.1283	3.04E–01	LABS
BLD# RETICULOCYTE AUTO	–0.0367	0.9639	0.8987 to 1.0339	3.05E–01	PROC
MRI BREAST BILATERAL	–0.0347	0.9659	0.9017 to 1.0346	3.22E–01	PROC
THER PX 1 + AREAS EA 15 MIN THER XERSS	–0.0326	0.9680	0.9049 to 1.0355	3.44E–01	PROC
GASES BLD PH DIR MEAS XCPT PLS OXIMTRY	–0.0508	0.9505	0.8546 to 1.0570	3.49E–01	PROC
CR	0.0378	1.0386	0.9507 to 1.1346	4.01E–01	LABS
TRFRN	–0.0332	0.9674	0.8930 to 1.0479	4.16E–01	LABS
ANTB HTLV-II	–0.1017	0.9033	0.7067 to 1.1546	4.17E–01	PROC
ANTB VARICELLA-ZOSTER	0.1040	1.1096	0.8606 to 1.4307	4.22E–01	PROC
CONSLTJ & REPRT SLIDES PREPARED ELSEWHERE	0.0247	1.0251	0.9639 to 1.0901	4.31E–01	PROC
IV NFS THER PROPH/DX ADDL SEQUENTIAL NFS > 1 HR	–0.0279	0.9725	0.9061 to 1.0438	4.40E–01	PROC

(continued on following page)

TABLE A3. All Least Absolute Shrinkage and Selection Operator Coefficients (continued)

Feature Name	Beta	OR	95% CI	*P*	Feature Type
HEP B CORE ANTB HBCAB TOT	0.0704	1.0730	0.8864 to 1.2988	4.70E–01	PROC
US VASC ACCESS SITS VSL PATENCY NDL ENTRY	0.0364	1.0370	0.9385 to 1.1458	4.75E–01	PROC
THERAPEUTIC PROPHYLACTIC/DX INJECTION SUBQ/IM	–0.0218	0.9784	0.9205 to 1.0400	4.83E–01	PROC
ANES INTRAPERITONEAL UPPER ABDOMEN W/LAPS	–0.0234	0.9769	0.9137 to 1.0445	4.93E–01	PROC
C-CNT MISC BDY FLUS XCPT BLD DIFFIAL CNT	0.0371	1.0378	0.9308 to 1.1571	5.03E–01	PROC
WBCFLD	–0.0245	0.9758	0.9080 to 1.0487	5.05E–01	LABS
ECHO TTHRC R-T 2D + M-MODE COMPL SPEC & COLOR DOP	0.0317	1.0322	0.9361 to 1.1382	5.25E–01	PROC
CHOL	–0.0639	0.9381	0.7643 to 1.1514	5.41E–01	LABS
IRON BNDNG CAP	–0.0660	0.9361	0.7570 to 1.1576	5.42E–01	PROC
ECG ROUTINE ECG W/LEAST 12 LDS TRCG ONLY W/O I & R	0.0654	1.0676	0.8566 to 1.3306	5.60E–01	PROC
KRAS GENE ANALYSIS VARIANTS IN CONDON 12 AND 13	0.0303	1.0308	0.9285 to 1.1442	5.70E–01	PROC
CONSLTJ & REPRT MATRL REQ PREPJ SLIDES	0.0182	1.0184	0.9564 to 1.0844	5.70E–01	PROC
VASC EMBOLIZE/OCCLUDE ORGAN	–0.0502	0.9510	0.7920 to 1.1420	5.91E–01	PROC
ARTL CATHJ/CANNULJ MNTR/TRANSFUSION SPX PRQ	–0.0250	0.9753	0.8879 to 1.0714	6.03E–01	PROC
CK	–0.0162	0.9839	0.9235 to 1.0482	6.15E–01	LABS
ANTB HTLV-I	–0.0715	0.9310	0.7029 to 1.2333	6.18E–01	PROC
RETICAB	–0.0153	0.9848	0.9270 to 1.0462	6.20E–01	LABS
PET IMAGING CT ATTENUATION SKULL BASE MID-THIGH	0.0167	1.0169	0.9514 to 1.0869	6.23E–01	PROC
MONO	0.0179	1.0181	0.9460 to 1.0956	6.32E–01	LABS
CYTP FINE NDL ASPIRATE I & R	0.0288	1.0293	0.9037 to 1.1723	6.64E–01	PROC
GLUC BDY FLU OTH/THN BLD	0.0331	1.0337	0.8753 to 1.2207	6.96E–01	PROC
IAAD EIA HIV 1 AG W HIV 1 HIV 2 ANTBDY SINGLE	0.0152	1.0153	0.9389 to 1.0980	7.03E–01	PROC
PATH CONSLTJ SURG CYTOLOGIC XM 1ST SIT	–0.0125	0.9876	0.9235 to 1.0561	7.14E–01	PROC
3-D RADIOTHERAPY PLAN	0.0223	1.0225	0.9024 to 1.1586	7.27E–01	PROC
ED VISIT - HIGH SEVERITY LIFE THREAT—LEVEL 5	–0.0212	0.9790	0.8688 to 1.1032	7.28E–01	PROC
GLOB	–0.0470	0.9541	0.7090 to 1.2839	7.56E–01	LABS
EVAL ORAL & PHARYNGEAL SWLNG FUNCJ	0.0104	1.0104	0.9374 to 1.0892	7.86E–01	PROC
ANTB HIV-1 & HIV-2 1 ASSAY	–0.0187	0.9815	0.8404 to 1.1462	8.13E–01	PROC
POST-OP/POST-OP F/U VISIT	–0.0086	0.9914	0.9097 to 1.0804	8.44E–01	PROC
COMPRHNSV HX/EXAM INIT HOSPITAL HIGH SEV 70 MIN	–0.0089	0.9911	0.8938 to 1.0991	8.66E–01	PROC
HGB	–0.0267	0.9737	0.6098 to 1.5548	9.11E–01	LABS
IAAD EIA HEP B SURF AG	–0.0110	0.9891	0.8145 to 1.2011	9.12E–01	PROC
RADJ TX MGMT 5 TXS	0.0069	1.0069	0.8498 to 1.1930	9.37E–01	PROC
BP_SYSTOLIC	–0.0074	0.9927	0.8261 to 1.1929	9.37E–01	VITALS
EVAL/MGMT OF EST PATIENT	–0.0016	0.9984	0.9400 to 1.0603	9.57E–01	PROC
LEVEL III-SURG PATH GROSS & MICROSCOPIC XM	0.0008	1.0008	0.9426 to 1.0626	9.79E–01	PROC
URNLS DIP STICK/TABLET RGNT AUTO MIC	0.0009	1.0009	0.9091 to 1.1019	9.86E–01	PROC

Abbreviations: DEMO, demographic and cancer-specific; DX, diagnoses; ED, emergency department; MRI, magnetic resonance imaging; OR, odds ratio; PROC, procedures; RX, medications; UTIL, utilization.

TABLE A4. Ablation Analysis AUROCs

Feature Set Ablated	AUROC	95% CI
None	0.7832	0.7636 to 0.8088
Demographics and cancer data	0.7787	0.7554 to 0.8019
Procedures	0.7850	0.7624 to 0.8076
Medications	0.7830	0.7601 to 0.8058
Labs	0.7798	0.7568 to 0.8028
Diagnoses	0.7887	0.7663 to 0.8111

Abbreviation: AUROC, area under the receiver operator curve.

