International Journal of Radiation Oncology biology • physics

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Clinical Investigation

A Machine Learning Model Approach to Risk-Stratify Patients With Gastrointestinal Cancer for Hospitalization and Mortality Outcomes

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Received Dec 3, 2020; Revised Mar 24, 2021; Accepted for publication Apr 19, 2021

Summary

Patients with gastrointestinal cancer undergoing abdominal or pelvic radiation treatment (RT) as part of multimodality care frequently experience unplanned hospitalizations due to acute toxicities and events. This study derived and validated a machine learning approach to predict

Purpose: Patients with gastrointestinal (GI) cancer frequently experience unplanned hospitalizations, but predictive tools to identify high-risk patients are lacking. We developed a machine learning model to identify high-risk patients.

Methods and Materials: In the study, 1341 consecutive patients undergoing GI (abdominal or pelvic) radiation treatment (RT) from March 2016 to July 2018 (derivation) and July 2018 to January 2019 (validation) were assessed for unplanned hospitalizations within 30 days of finishing RT. In the derivation cohort of 663 abdominal and 427 pelvic RT patients, a machine learning approach derived random forest, gradient boosted decision tree, and logistic regression models to predict 30-day unplanned hospitalizations. Model performance was assessed using area under the receiver operating characteristic curve (AUC) and prospectively validated in 161 abdominal and 90 pelvic RT patients using Mann-Whitney rank-sum test. Highest quintile of risk for hospitalization was defined as "high-risk" and the

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Disclosures: Relevant to the submitted work: G.L.S. receives research support from the National Cancer Institute (NIH/NCI K07CA211804) and a family member has equity interest in Oncora Medical. D.L. is an equity holder in, director of, and employee of Oncora Medical, Inc. C.B. is an equity holder in, director of, and employee of Oncora Medical, Inc. C.A. is an equity holder in and an employee of Oncora Medical, Inc. B.D.S. has a royalty and equity interest in Oncora Medical, Inc. Other conflicts of interest are not relevant to the submitted work.

Research data not available at this time.

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.ijrobp.2021.04.019.

Int J Radiation Oncol Biol Phys, Vol. 111, No. 1, pp. 135–142, 2021
0360-3016/$ - see front matter
https://doi.org/10.1016/j.ijrobp.2021.04.019

high-risk patients. Validation models discriminated high- versus low-risk patients. In abdominal RT patients, frequency of hospitalization was 39% versus 9% in predicted high- versus low-risk groups ($P < .001$). In pelvic RT patients, frequency of hospitalization was 33% versus 8% ($P = .002$).

remainder "low-risk." Hospitalizations for high- versus low-risk patients were compared using Pearson's χ^2 test and survival using Kaplan-Meier log-rank test.

Results: Overall, 13% and 11% of patients receiving abdominal and pelvic RT experienced 30-day unplanned hospitalization. In the derivation phase, gradient boosted decision tree cross-validation yielded AUC = 0.823 (abdominal patients) and random forest yielded AUC = 0.776 (pelvic patients). In the validation phase, these models yielded AUC = 0.749 and 0.764, respectively ($P < .001$ and $P = .002$). Validation models discriminated high- versus low-risk patients: in abdominal RT patients, frequency of hospitalization was 39% versus 9% in high- versus low-risk groups ($P < .001$) and 6-month survival was 67% versus 92% ($P = .001$). In pelvic RT patients, frequency of hospitalization was 33% versus 8% ($P = .002$) and survival was 86% versus 92% ($P = .15$) in high- versus low-risk patients.

Conclusions: In patients with GI cancer undergoing RT as part of multimodality treatment, machine learning models for 30-day unplanned hospitalization discriminated high- versus low-risk patients. Future applications will test utility of models to prompt interventions to decrease hospitalizations and adverse outcomes.

Introduction

Unplanned hospitalizations in patients with cancer are a costly and frequent adverse outcome, with cancer patients undergoing multimodality treatment especially at risk.[1,2] Approximately 30% of patients with cancer experience unplanned hospitalization within the first year after diagnosis,[3] and risks of hospitalization persist during the entire cancer care delivery trajectory.[4,5] Patients with gastrointestinal (GI) cancers, including those undergoing radiation treatment (RT), are at particularly high risk for unplanned hospitalizations, due to the frequent need for multimodality treatment in this population especially for advanced stage cancers, leading to fluid and electrolyte abnormalities, infection, or significant symptoms that may be further complicated by patients' frailty or comorbidities.[3,5-10] A prior study observed a 30-day hospital readmission rate in patients with GI cancer as high as 13% to 22% after index hospitalization.[5]

Although the causes of unplanned hospitalizations and acute care utilization in cancer patients may be potentially avoidable or amenable to early mitigation, tools to help prospectively identify patients at high-risk are still needed.[11] The factors that play a role in a patient's risk of unplanned hospitalization during or after radiation therapy are wide-ranging, including sociodemographic characteristics, clinical characteristics, such as comorbidity and tumor characteristics, and treatment variables such as chemotherapy regimens, surgical details, and radiation therapy. Machine learning (ML) may provide a robust and useful strategy to account for complex factors predicting patients' risk of hospitalization, with further promise if applied for patient risk stratification and intervention.[12] However, in a recent study that derived an ML predictive model for unplanned hospitalizations in cancer undergoing RT, the model was less discriminatory for patients with GI cancer, with higher frequency of false positive predictions.[8] Discriminating high- versus low-risk patients GI with cancer remains a persistent challenge for ML-based risk stratification, due to their overall high frequency of needing acute care. Therefore, we sought to derive a novel predictive model using a ML approach focused on patients with GI cancer, incorporating risk factors ascertained before the start of abdominal or pelvic RT, to predict 30-day unplanned hospitalizations in this patient group, which frequently undergoes multimodality treatment. We also sought to evaluate the model performance in prospectively identifying patients as low- versus high-risk in a validation cohort. Finally, we secondarily sought to evaluate overall survival in patients classified in the validation analysis as low- versus high-risk patients.

Methods and Materials

Patient sample and data sources

The M.D. Anderson Cancer Center Institutional Review Board approved this study. We included consecutive patients ages ≥18 years old with a diagnosis of GI malignancy treated with abdominal (ie, stomach or gastroesophageal junction, pancreatic, hepatobiliary, or related lymph node sites of the abdomen) or pelvic (ie, anus, rectum, or related lymph node sites of the pelvis) RT as a component of their cancer therapy at our institution between March 2016 and January 2019, for a total of 1341 consecutive cases treated with RT targeting abdominal or pelvic radiation fields. Candidate features tested in predictive models were extracted from electronic data sources: the radiation treatment prescription and field variables were obtained from the radiation record and verify system and institutional radiation treatment electronic data workflow support database, and patient, sociodemographic, comorbidity, and clinical variables (eg, laboratory values, cancer-directed

treatment, stage), using automated extraction from the electronic medical record (EMR; Epic). Data across sources were integrated using a proprietary oncology analytics platform (Oncora Analytics, Philadelphia, PA) for analytical modeling.[13]

Predictor and outcome variables

We extracted 787 predefined candidate clinical and treatment variables, including details about demographics (9), medical history (389), laboratory values within 30 days of RT (classified based on the institution's laboratory ranges for normal values; 217), tumor/stage (31), surgery (104), chemotherapy (19), and radiation (18), which were candidate features for training predictor models (Appendix E1). As a descriptor variable for treatment, multimodality cancer care was defined as a cancer-directed surgery within 90 days before to 90 days after RT, or chemotherapy within 180 days before to 180 days after RT.

The primary outcome extracted from the EMR was claims coding any unplanned hospitalization during RT through 30 days after the date of RT completion.[14] Planned hospitalizations, for example, expected admissions for curative cancer surgery were not categorized as an unplanned hospitalization. Charges were obtained from billing records. The secondary outcome of all-cause mortality was extracted from the EMR vital status and tumor registry records. To ensure the quality and accuracy of EMR extracted outcomes definition, 15 randomly selected episodes of care were manually reviewed, abstracted, and verified for causes of hospitalization (K.C.).

Statistical analysis

Among 824 abdominal cases and 517 pelvic cases, separate cohorts were analyzed for the model derivation phase (including patients with RT between March 2016 and July 2018) and model validation phase (including patients with RT between July 2018 and January 2019). The derivation cohorts included 663 abdominal RT patients and 427 pelvic RT patients; validation cohorts included 161 abdominal RT patients and 90 pelvic RT patients. Descriptive statistics were calculated to describe percentage of unplanned hospitalizations and top admission diagnoses (other than "cancer").

In the abdominal and pelvic RT derivation cohorts, random forest, gradient boosted decision tree, and logistic regression models were each derived for the outcome of 30-day unplanned hospitalizations. To avoid overfitting, variables with very low variance (variance below a threshold of 0.15) were removed. Model selection was performed using 5-fold cross validation, using area under the receiver operating characteristic curve (AUC) to measure performance. The best performing models were then tested on validation cohorts, where AUC was used to measure performance. The Mann-Whitney rank-sum test was used to compare the models' discernment for the outcome of hospitalization versus the null (AUC = 0.5), representing no discernment for the outcome. A predefined AUC threshold of 0.7 was considered clinically meaningful.[15] The bootstrapped confidence intervals for AUC values were based on 1000 resamples. In sensitivity analyses, parsimonious models limited to the top 50 performing features were derived for the abdominal and pelvic derivation validation cohorts using the same model derivation methods as outlined. For the best performing parsimonious model in each cohort, AUCs were also calculated based on the respective validation sets.

Within each validation cohort, patients were classified as "high-risk" for 30-day unplanned hospitalization based on an a priori definition of patients in the highest quintile (20th percentile) of predicted hospitalization risk. Remaining patients were classified as "low-risk." We used the Pearson's χ^2 test to compare frequencies of observed versus expected hospitalizations in high- versus low-risk groups and compared observed and expected hospitalization outcomes within groups. We additionally conducted sensitivity analyses with patients classified as high- versus low-risk using alternate cutpoints (15th percentile and 25th percentile) for comparison with the primary selected cutpoint of 20th percentile.

For survival analysis, time to death was calculated from the date of RT start and cases were censored at last date of follow-up. Survival outcomes were estimated using the Kaplan-Meier method and log-rank test, comparing survival in expected high- versus low-risk groups. Analyses were conducted using SAS version 9.3 (Cary, NC) using 2-tailed test and P value $< .05$ considered statistically significant.

Results

Patient characteristics

Median age of patients in the abdominal cohort was 66 years old (interquartile range [IQR], 59-73) and 60% were men. The median age in the pelvic cohort was 57 years old (IQR, 49-66) and 48% were men. Median duration of follow-up for the validation abdominal and pelvic cohorts were 7.9 months (IQR, 4.5-10.2) and 9.1 months (IQR, 6.7-10.4), respectively. Almost all patients, 93%, received a multimodality cancer treatment trajectory, with surgery (within 90 days) and chemotherapy (within 180 days) delivered during patients' cancer care trajectory. A total of 81% received chemotherapy concurrent with the RT course. Additional patient characteristics are detailed in Table 1.

Unplanned hospitalizations within 30 days of completing abdominal or pelvic RT

Frequency of 30-day unplanned hospitalizations for the entire cohort was 12.3%. Specifically, frequency was 13.3% in the abdominal cohort and 10.7% in the pelvic cohort. Among these hospitalizations, median length of

Table 1 Patient, tumor, and treatment characteristics for the entire study cohort (N = 1341)

Characteristic	Abdominaln n of 824 (%)	Pelvic n of 517 (%)
Age (y)		
Median (IQR)	66.3 (58.7, 73.2)	57.6 (49.4, 65.9)
Sex		
Male	492 (60)	248 (48)
Female	332 (40)	269 (52)
Race and ethnicity		
White, non-Hispanic	561 (68)	347 (67)
Black, non-Hispanic	58 (7)	50 (10)
Hispanic	105 (13)	71 (14)
Other	100 (12)	49 (9)
Insurance		
Medicare	427 (52)	148 (28)
Private	327 (40)	309 (60)
Medicaid	4 (<1)	10 (2)
Other	66 (8)	50 (10)
Stage		
I	106 (13)	35 (7)
II	181 (22)	61 (12)
III	227 (27)	212 (41)
Recurrent/M+	310 (38)	209 (40)
Treatment intent		
Curative	488 (59)	404 (78)
Consolidative	184 (22)	29 (6)
Palliative	153 (19)	84 (16)
Treatment technique		
3D	202 (25)	265 (51)
IMRT	515 (62)	249 (48)
SBRT	105 (13)	0 (0)
Proton	2 (<1)	3 (<1)
Radiation treatment dose and fractionation		
Median dose (Gy) (IQR)	50.0 (36.0, 60.0)	50.4 (39.0, 50.4)
Median fractions (IQR)	15 (10, 25)	27 (25, 28)
Concurrent chemotherapy		
Yes	483 (59)	421 (81)
No	341 (41)	96 (19)
Serum sodium (mEq/L)		
Median (IQR)	141 (138, 143)	141 (139, 143)
Serum chloride (mEq/L)		
Median (IQR)	103 (101, 105)	103 (101, 105)
Serum albumin (gm/dL)		
Median (IQR)	4.0 (3.7, 4.2)	4.2 (3.9, 4.4)
Hemoglobin (gm/dL)		
Median (IQR)	11.9 (10.6, 13.1)	12.6 (11.2, 13.8)

Abbreviations: 3D = 3-dimensional radiation therapy; IMRT = intensity modulated radiation therapy; IQR = interquartile range; M+ = metastatic disease; SBRT = stereotactic body radiation therapy.

stay was 5 days (IQR, 3-10). Common causes of hospitalization included fever and infection, abdominal and chest pain, nausea with vomiting, diarrhea, constipation, and gastrointestinal hemorrhage (Table 2). Among patients who had unplanned hospitalization, the excess health care charges through 30-day follow-up for abdominal RT patients who were hospitalized versus not hospitalized was $52,435 and for pelvic RT patients was $49,402.

Table 2 Causes of unplanned hospitalization for patients who received abdominal or pelvic RT

Patients who received abdominal RT	n (of 49)	(%)
Fever	8	(16)
Abdominal pain	7	(14)
Cholangitis	7	(14)
Nausea with vomiting	7	(14)
Acute kidney failure	4	(8)
Obstruction of bile duct	4	(8)
Altered mental status	3	(6)
Management of vascular access device	3	(6)
Malignant neoplasm of pancreas	3	(6)
Pneumonia	3	(6)
Patients who received pelvic RT	n (of 22)	(%)
Malignant neoplasm of rectum	5	(23)
Diarrhea	4	(18)
Gastrointestinal hemorrhage	4	(18)
Pain	3	(14)
Chest pain	2	(9)
Constipation	2	(9)
Malignant neoplasm of anal canal	2	(9)

Abbreviation: RT = radiation treatment.

Model derivation and validation in the abdominal RT cohort

The most common primary diagnoses in the abdominal RT cohort were 49% pancreatic, 19% hepatobiliary, and 13% gastric cancer. The cross-validation AUC values in the derivation cohort were 0.823 for gradient boosted decision trees, 0.806 for random forest, and 0.808 for logistic regression. In the validation cohort, the best performing model (gradient boosted decision tree) demonstrated good performance with an AUC of 0.749 (95% confidence interval [CI], 0.595-0.822; $P < .001$). Variables with the highest feature importance in this predictive model included: treatment site (pancreas, stomach, liver, or other), and key laboratory values within the 30 days before RT (including sodium, high density lipoproteins, calcium, aspartate aminotransferase, hematocrit, albumin, platelets, neutrophils, chloride, and alkaline phosphatase), as well as RT dose.

Model derivation and validation in the pelvic RT cohort

The most common primary diagnoses in the pelvic RT cohort were 76% rectal and 18% anal cancer. The cross-validation AUC values in the derivation cohort were 0.771 for gradient boosted decision trees, 0.776 for random forest, and 0.753 for logistic regression. In the validation cohort, the best performing model (random forest) demonstrated good performance, with an AUC of 0.764 (95% CI, 0.601-0.871; $P = .002$). Variables with the highest feature importance included: key laboratory values within the 30 days before RT (including chloride, hemoglobin, sodium, total

protein, hematocrit, platelets, potassium, and sodium), body mass index, and days spanning RT duration.

See Table E1 for top feature importance for the best performing models in the abdominal RT and pelvic RT cohorts in, Figure E1 for calibration curves for these models, and Table E2 for AUCs for the alternate model algorithms in the validation cohorts. A comparison of patient characteristics for derivation and validation populations in Table E3. In sensitivity analyses, parsimonious models (limited to the top importance 50 features Table E1) were derived and then validated. The AUC of 0.694 (gradient boosted decision tree) for the abdominal RT validation cohort and the AUC of 0.696 (random forest) for the pelvic RT validation cohort using this parsimonious approach. AUCs for the alternate parsimonious model algorithms are in Table E2.

Outcomes in high- versus low-risk patients for 30-day unplanned hospitalization in the validation cohort

In patients undergoing abdominal RT, the actual (observed) frequency of 30-day unplanned hospitalizations was 39.4% versus 9.4% in the high-risk versus low-risk patients ($P < .001$). These observed frequencies of hospitalization were similar to the expected hospitalization frequencies (mean prediction; 30.1% vs 3.8%, respectively). In patients undergoing pelvic RT, the observed unplanned hospitalization frequency was 33.3% versus 8.3% in high- versus low-risk patients ($P = .002$). Expected frequencies (mean prediction) were 27.9% versus 7.6%, respectively (Fig. 1a-b). See Table E4 for within risk strata comparisons and Table E5 for sensitivity analysis of alternate cutpoints to define the threshold definition for high- versus low-risk for hospitalization.

In the validation cohorts, median overall survivals were not yet reached (Fig. 2a-b). For patients receiving abdominal RT, 6-month actuarial survival for patients with high- versus low-risk for 30-day unplanned hospitalization were 67% versus 92% ($P = .001$). For patients receiving pelvic RT, 6-month actuarial survival for high- versus low-risk patients was 86% versus 96% ($P = .15$).

Discussion

In this cohort of patients with GI cancer, tailored ML models trained to predict 30-day unplanned hospitalizations were clinically meaningful (AUC >0.7), and in prospective validation, effectively discriminated high- versus low-risk patients. The observed frequency of hospitalization among high-risk patients with GI cancer after abdominal or pelvic RT was substantial, approximately 30% in both groups. Although these hospitalizations were emergent or urgent (not elective), many causes of admission were potentially avoidable, including pain, infection, and GI symptoms. Although models were trained to predict the acute event of hospitalizations, the data provided a promising signal that

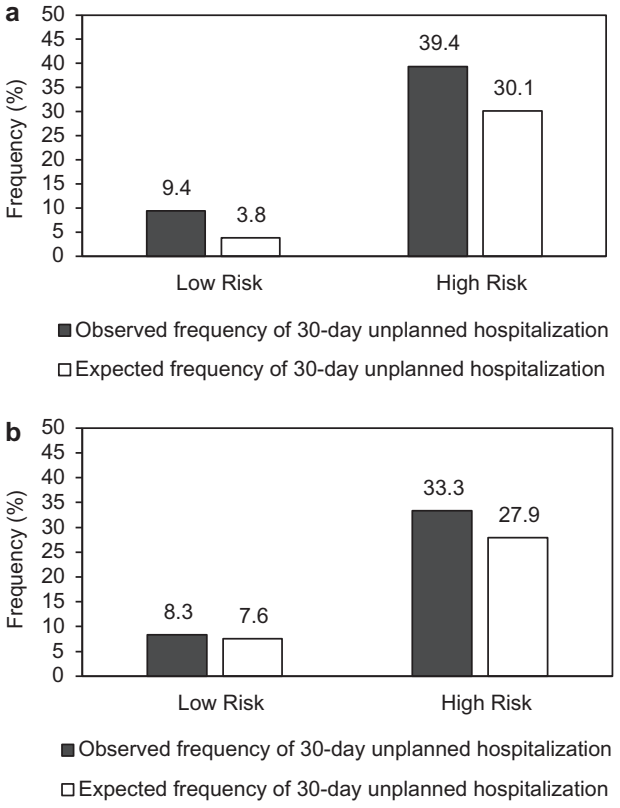

Fig. 1. Unplanned hospitalization: observed and mean expected 30-day frequency of unplanned hospitalizations in predicted low-risk and high-risk patients after receiving (a) abdominal radiation treatment or (b) pelvic radiation treatment.

the models could further effectively discriminate subsequent all-cause mortality risk, with significant differences seen in the abdominal RT patients and marginal significance for pelvic RT patients. The predictive power of this risk-stratification approach for survival outcomes will require additional follow-up, but these early results suggest that future iteration and application of these models in clinical settings for early risk prediction and symptom intervention could have an effect not only on health care utilization but also potentially on key clinical outcomes such as mortality.[16,17]

Risks and predictors of acute care events (hospitalizations and emergency room visits) in cancer patients after chemotherapy have been examined in prior studies, although less so after RT.[6,8,10,11,17-20] Prior studies identified risk factors associated with hospitalizations, including age, comorbidity, abnormal laboratory values, recent chemotherapy, and pain or patient reported symptoms.[18,21-23] However, beyond classical models used in prior predictive models and algorithms, ML methods such as tree-based models, ensemble methods, and neural networks now represent a novel approach that could improve predictions of acute care events after cancer therapy.[6,8,24,25] Results from our model specifically trained on patients with GI cancer, primarily comprised of patients with primary diagnosis of pancreas, hepatobiliary, gastric,

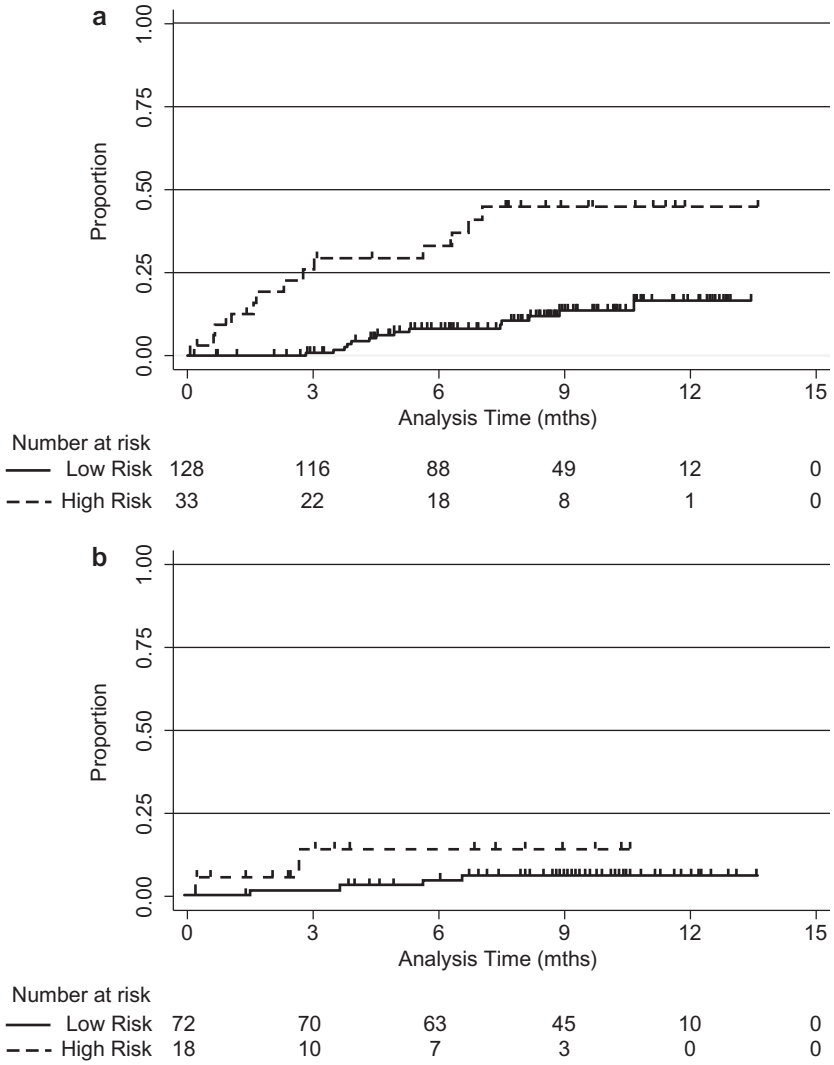

Fig. 2. All-cause mortality in predicted low-risk versus high-risk patients after receiving (a) abdominal radiation treatment ($P < .001$) or (b) pelvic radiation treatment ($P = .15$).

rectal, or anal cancer, almost all receiving multimodality treatment, building on the recent data indicating that patients with GI cancer are at especially high risk for hospitalization, for example, 13% to 22% within 30 days of an index hospitalization in a prior study.[5] In a prior ML model, prediction for acute events was trained on patients with cancers of all sites, and the model performed with less precision in GI patients.[8] Subsequent validation and application of that model in a prospective, randomized study confirmed that GI patients were disproportionately at highest risk for hospitalization.[12] Those randomized results suggested that in a general cohort of patients with cancer comprised of many different disease or treatment sites, patients with GI cancer tended to be categorized relatively homogeneously as high-risk, compared with lower risk patients for hospitalization such as those with breast cancer.[12] Our study advances from the prior findings by using a tailored model to better stratify an overall high-risk group of GI patients for hospitalization, in whom accurately predicting those patients truly requiring high intensity monitoring or intervention is particularly difficult.[8] Results of our study highlight the utility of the data analytics and integration platform with automated EHR-based data extraction for this tailored modeling approach. Our results improve both the model fit and the clinical applicability of findings for GI patients as a resource-intensive patient population. More accurately discerning subsets of high- or low- risk GI patients is necessary to promote high-value GI cancer care, especially when resources are finite for applying the high-intensity acute clinical evaluation and toxicity management approach that is resource intensive.[12]

Our findings additionally demonstrate that the RT delivery setting serves as a useful setting for both risk prediction and intervention and a unique opportunity for deriving and applying ML-based acute event risk prediction, given the high density of health care interactions during the RT course and the sequencing of RT within the multimodality therapeutic strategies. Together, these characteristics of the RT care delivery setting, especially for high-risk populations, such as patients with GI cancer receiving multimodality care, represent an opportunity to proactively assess and

intervene in patients using strategies such as enhanced care coordination, standardized pathways for symptom management, and early use of palliative therapy.[2] Future implementation testing seeks to determine prospective feasibility of implementing a complex model with a high number of features on a wider scale. Embedding risk score calculation into usual workflows through integration with electronic medical record systems is another key component of implementation.

Our findings are therefore relevant to the recently identified health care delivery priority of reducing acute care events in cancer patients, dominated by unplanned hospitalizations, which exact tremendously costly resources from the health care system, up to 48% of national spending on cancer care, and have triggered the emergence of reducing unplanned hospitalization in this population as a key quality cancer care delivery goal of Centers for Medicare and Medicaid Services.[2] Future prospective application of this model tailored for GI patients will evaluate for the contribution to reducing acute care events and contributing to value in care.

A limitation of this analysis is that hospitalizations were assessed at our single institution and therefore could have underreported hospitalizations occurring outside the institution, decreasing sensitivity of findings.[26] The external validation and prospective testing of the proposed model to inform intervention are needed, and this work is ongoing. The implementation testing needed will include applying the more complex models as tested in this study, compared with parsimonious models as presented as sensitivity results, given the tradeoff between model fit versus the complexity of incorporating a large number of feature data. Implementation testing will also include applying a similar methodologic approach to derive models to understand, which common important features persist across different clinical settings versus which local features are uniquely needed to tailor a model to a specific health care delivery environment or patient population. Future model iterations can also account for incoming clinical data, beyond the features extracted in the pre-RT time span, thereby being able to better incorporate sudden changes in the patient's condition that could meaningfully change the risk prediction and improve precision of the risk prediction.

Conclusions

Machine learning models tailored to GI cancer patients demonstrated good performance in training and validation cohorts for predicting risks of unplanned hospitalizations within 30 days of RT. In prospective validation, high-risk patients identified by these tailored models had approximately 30% hospitalization risk and trend toward worse all-cause mortality. Future pragmatic tools incorporating tailored ML model findings, deployed in clinical settings, may represent a valuable opportunity to prospectively identify patients with high-risk GI cancer and implement interventions to mitigate adverse outcomes.

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