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Predicting Persistent Opioid Use, Abuse and Toxicity Among Cancer Survivors

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Running Title: Persistent opioid use in cancer survivors

Abstract

Background: While opioids play a critical role in the management of cancer pain, the ongoing opioid epidemic has raised concerns regarding their persistent use and abuse. We lack data-driven tools in oncology to understand the risk of adverse opioid-related outcomes. This project seeks to identify clinical risk factors and create a risk score to help identify patients at risk of persistent opioid use and abuse.

Methods: Within a cohort of 106,732 Veteran cancer survivors diagnosed between 2000 and 2015, we determined rates of persistent post-treatment opioid use, diagnoses of opioid abuse or dependence, and admissions for opioid toxicity. A multivariable logistic regression model was used to identify patient, cancer, and treatment risk factors associated with adverse opioid-related outcomes. Predictive risk models were developed and validated using a least absolute shrinkage and selection operator (LASSO) regression technique.

Results: The rate of persistent opioid use in cancer survivors was 8.3% (95% CI=8.1 - 8.4%), the rate of opioid abuse or dependence was 2.9% (95%CI=2.8-3.0%), and the rate of opioid-related admissions was 2.1% (95%CI=2.0-2.2%). On multivariable analysis, several patient, demographic, cancer and treatment factors were associated with risk of persistent opioid use. Predictive models showed a high level of discrimination when identifying individuals at risk of adverse opioid-related outcomes including persistent opioid use (area under curve [AUC]= 0.85), future diagnoses of opioid abuse or dependence (AUC=0.87) and admission for opioid abuse or toxicity (AUC=0.78).

Conclusion: This study demonstrates the potential to predict adverse opioid-related outcomes among cancer survivors. With further validation, personalized risk stratification approaches could guide management when prescribing opioids in cancer patients.

Key Words: Opioid use, opioid abuse, opioid dependency, opioid toxicity, cancer survivorship

Pain remains one of the most feared and burdensome symptoms associated with cancer, and its curative therapies.[1] More than half of cancer patients undergoing curative treatment experience pain rated as moderate to severe, warranting opioid use.[2,3] Despite the accepted role of opioid analgesics in acute pain relief, the utility of opioid use in chronic pain (*i.e.* pain lasting longer three to six months) remains controversial.[4,5] Chronic opioid use can lead to diminishing analgesic efficacy with the possibility of toxicity including depression, sedation, loss of concentration, hyperalgesia and hypogonadism.[4,6,7] Additional known risks with prolonged opioid use include dependence, misuse, abuse, drug diversion, and unintentional overdosing.[8] Furthermore, the ongoing opioid epidemic has raised concerns among patients and oncology providers regarding addiction and misuse.[1] With an estimated 13.7 million cancer survivors in the United States and two-thirds of newly diagnosed cancer patients living more than 5 years, a better understanding of persistent opioid use, abuse and toxicity in oncology patients is imperative.[6,9]

Optimal pain management with opioids requires a patient-specific assessment of benefits and risks.[7,8] Along these lines, the American Society of Clinical Oncology (ASCO) recommends a risk stratified approach to pain management and prescribing opioids.[6] Specific risk mitigation strategies include adherence monitoring, drug screening, alternative pain management strategies, judicious opioid use and referral to pain specialists.[6] Current guidelines for risk stratification, however, are based on expert opinion or instruments validated in non-oncology cohorts that may omit risk factors relevant to cancer patients.[10–13] An evidence-based risk stratification approach could help clinicians better identify those at risk of adverse opioid-related events who might benefit from proactive adherence monitoring and

mitigation. The purpose of this study was to determine rates and factors associated with persistent opioid use, diagnoses of opioid abuse, and admissions for opioid toxicity among a large cohort of cancer survivors who received curative intent cancer therapy. Additionally, we created and validated predictive models to help provide a clinically applicable approach to identifying patients at risk.

Methods

Data source

Patients were selected from the Veterans Affairs (VA) Informatics and Computing Infrastructure (VINCI) database.[14] VINCI is a comprehensive nationwide database that contains detailed electronic health record information on all Veterans within the VA healthcare system. VINCI contains information on patient demographics, past medical history, medications, procedures, diagnoses, emergency room visits, clinic visits, and hospitalizations.[14] Among cancer patients additional data are collected by trained cancer registrars regarding stage at diagnosis, treatment and recurrence in accordance with standardized protocols from the American College of Surgeons.[15]

This study cohort included patients diagnosed with one of the twelve most common non-cutaneous, non-hematologic malignancies in VA patients (bladder, breast, colon, esophagus, stomach, head and neck, kidney, liver, lung, pancreas, prostate, or rectal cancer) from 2000 to 2015, treated with definitive local therapy (surgery, radiation therapy (RT) or both) and alive without recurrence two years after the initiation of treatment (**Supplementary Figure 1**). Patients with metastatic disease or unknown stage at diagnosis were excluded. This

study was reviewed and approved by the VA Health Care System. Waivers of consent and authorization were granted by the Institutional Revie Board (IRB) and the Research and Development Committee of the VA Health Care System (IRB Protocol Number 150169).

Covariates

Baseline patient, demographic and cancer data were extracted from tumor registry data.[16] Patient ZIP codes were used to obtain regional high school graduation rates, median household income level, and population density (urban or rural).[17,18] International Classification of Disease (ICD) codes (9th or 10th edition) in the year prior to the start of cancer treatment were used to define the NCI-adapted Charlson Comorbidity Index (CCI), which excludes cancer-related comorbidities. Similarly, ICD-9 or ICD-10 codes were used to capture pre-cancer diagnoses of depression, alcohol abuse, non-opioid drug abuse, or opioid abuse.[19–21] Additionally, we identified 'high risk' psychiatric conditions prior to cancer diagnosis which included bipolar disorder, schizophrenia, obsessive compulsive disease (OCD) and attention deficit disorder (ADD) as defined by Webster and colleagues.[10,22] Body mass index at the time of cancer diagnosis was classified as healthy weight (18.5-25 kg/m^2), underweight (< 18.5 kg/m^2) or overweight (> 25 kg/m^2).[23]

Opioid use

Opioid use was determined from dispensed medication data in the VA outpatient pharmacy database. Similar to prior studies, patients were defined as *opioid naïve* if no prescriptions were filled from one to twelve months prior to their first day of treatment.[24–26]

Prior chronic opioid use was defined as having filled equal to or more than 120 days' supply of opioids between one to twelve months before treatment, or three opioid prescriptions from three to six months prior to treatment.[24,25,27] *Intermittent opioid use* was defined as any opioid use from one to twelve months prior to treatment that did not meet criteria for chronic opioid use.[24] Opioid use in the *diagnosis and treatment period* included any use extending from one month prior to the first day of treatment to 3 months after treatment.[24,25]

Endpoints

The primary endpoint of *persistent opioid use* was defined with the previously published threshold of having filled ≥ 120 days' supply or ≥10 opioid prescriptions from one to two years after the start of curative treatment.[28] This interval was selected as a time when patients should have completed primary and adjuvant cancer therapy and recovered from acute toxicity. Secondary endpoints included *diagnoses of opioid abuse or dependence* identified from ICD-9 and ICD-10 diagnosis codes, and *admissions for opioid abuse, dependence or toxicity* identified from inpatient admissions after the diagnosis date. Diagnoses of opioid abuse and dependence were analyzed together for the purposes of this study and approximate mild and moderate/severe opioid use disorder , respectively, as defined by the Diagnostic and Statistical Manual of Mental Disorders (DSM-5).[29,30]

Statistical analysis

Baseline covariates were compared between patients that became persistent opioid users and those that did not using a chi-squared test for categorical variables and a Student's t-

test for continuous variables. We used standard multivariable logistic regression models to identify associations between our study endpoints and predictive variables. We chose variables for the multivariable models *a priori* which included patient, demographic, clinical, and treatment-related variables. Because toxicities for surgery, radiation and chemotherapy vary by cancer type and stage, we suspected a potential interaction between these factors. Accordingly, we tested for interaction terms between cancer type and stage and treatment factors in our regression models. Statistical analyses and modeling were performed using R version 3.5.1 (https://cran.r-project.org/). All tests were two-sided and a P value of less than 0.05 was considered statistically significant.

Predictive Modeling

For the predictive models only, imputation of missing variables for predictive modeling was accomplished via multivariate imputation by chained equations (MICE) approach.[31] Covariates were assumed to be missing at random and distribution of missing data was evaluated using the MICE R package. In total, imputation replaced missing data for alcohol use (14.5% missing), tobacco history (14.4% missing), BMI category (3.5% missing), median income (2.3% missing), high school graduation rate (1.9% missing), and rural status (0.3% missing). A sensitivity analysis was also performed by including only complete cases for the logistic regression and predictive modeling which generated similar findings (results not shown). The cohort was randomly divided 1:1 into a training and test (validation) data set. Covariates and interaction terms described above were selected as potential predictor variables in Least Absolute Shrinkage and Selection Operator (LASSO) logistic regression models for each study

endpoint.[32,33] LASSO regression was selected as a robust supervised-learning approach that would facilitate variable selection for this high-dimensional dataset. We optimized the weighted penalty term (ƛ) using 10-fold cross validation, and selecting a final ƛ that was one standard error greater than the best-performing ƛ, as per standard practice.[34] We also explored simpler and more parsimonious models by increasing ƛ until five covariates remained. The predictive models were created with the training data set, and discriminative ability of the risk score was assessed in the test data set using a Receiver Operator Curve (ROC). An area under the curve (AUC) of 0.5 indicates the model was no better than random chance, and an AUC of 1.0 indicates perfect discrimination. A predictive risk score was developed using the linear predictors from the LASSO logistic regression model. For the persistent opioid use prediction model only, we categorized patients into predicted risk groups (low: ≤5% vs. intermediate: > 5 and ≤ 25% vs. high >25%) based on cutoffs determined to be clinically relevant *a priori.* The simpler predictive models had similar discriminative ability as the complete models, therefore we present the simpler models for each endpoint in the results section and included the more complex models in the **Supplementary Table 2** and **Supplementary Figure 2**).

Results

Rates of Adverse Opioid Events

Among the 106,732 cancer survivors in this study the overall incidence of persistent post-treatment opioid use was 8.3% (95% CI, 8.1 - 8.4%) which varied by cancer type ranging from a low of 5.3% (5.1-5.5%) in prostate cancer patients to a high of 19.8% (17.2-22.5%) in liver cancer patients (**Figure 1**). The rates of persistent opioid use after treatment varied

substantially by a patient's history of opioid use prior to their cancer diagnosis. The persistent post-treatment opioid use rates were lowest for opioid naïve patients (3.5% [95% CI, 3.3-3.6%]) followed by prior intermittent users (15.0% [14.4-15.6%]), and prior chronic users (72.2% [70.9-73.4%]). Among naïve patients, the rates of opioid use varied by whether patient's received opioids during the diagnostic and treatment period. Those prescribed an opioid during the diagnostic and treatment period had rates of persistent post-treatment use of 6.2% (6.0-6.5%), compared to 1.5% (1.4-1.6%) of those that did not receive a prescription. The rate of post-treatment diagnoses of opioid abuse or dependence was 2.9% (2.8-3.0%), and opioid-related admissions occurred in 2.1% (2.0-2.2%) of patients.

Factors associated with opioid-related endpoints

On multivariable analysis, several factors were associated with the risk of persistent opioid use (**Figure 2**). Younger age, white race, unemployment at the time of cancer diagnosis, lower median income, increased comorbidity, and current or prior tobacco use were all associated with increased adjusted odds of persistent opioid use. Prior diagnoses of alcohol abuse, non-opioid drug abuse, opioid abuse, and depression were associated with increased odds. Prior history of chronic opioid use and prior intermittent use were associated with substantially increased odds of persistent opioid use. Among opioid naïve patients those without an opioid prescription during the diagnostic or treatment period had a lower risk persistent opioid use compared to those who received an opioid prescription. Bladder, breast, esophagus, stomach, head and neck, liver, lung and pancreas cancer were associated with higher odds compared to prostate cancer.

Stratified analyses evaluating the influence of AJCC stage, local treatment, and chemotherapy on the risk of persistent opioid use is presented in **Supplementary Table 1**. In general, stage, local treatment, and chemotherapy use were not associated with persistent opioid use outside of a few disease-site specific scenarios. Higher stage colon, lung, and head and neck cancer patients had an increased odds of persistent opioid use compared to lower stage patients. Definitive radiation therapy was associated with an increased odds of persistent opioid use compared to definitive surgery in prostate and lung cancer patients. Kidney cancer patients receiving chemotherapy had an increased odds of persistent opioid use compared to those who did not receive chemotherapy.

Factors associated with the risk of future opioid abuse or dependence and opioid-related admissions are presented in **Figure 2**.

Risk score to predict adverse opioid-related endpoints

Our LASSO regression to create predictive risks scores identified patient, tumor, and treatment-related factors associated with the risk of the three opioid-related endpoints. Predictive covariates varied across the three different models (see **Table 2** for predictive factors). Use of chemotherapy was a risk factor associated with an increased adjusted risk of all three opioid-related outcomes. Other factors associated with an increased risk varied by model, though included history of depression, prior opioid use, prior opioid abuse, alcohol abuse, and non-opioid drug abuse. Age was associated with a decreased risk of adverse outcomes. The individual models demonstrated a relatively high level of discrimination in predicting persistent opioid use (AUC = 0.85), opioid abuse or dependence (0.87), and opioid-related admission

(0.78). The predictive models for persistent opioid use effectively stratified patients into low, intermediate and high risk groups (**Figure 3b**). The full predictive model demonstrated minimally improved discrimination for persistent opioid use (AUC = 0.87), opioid abuse or dependence (0.88), and opioid-related admissions (0.79) (see **Supplementary Table 2** for predictive factors). We developed an online risk tool for these predictive models (www.CancerOpioidRisk.org) to assist with clinical implementation.

Discussion

Opioids are an effective and often irreplaceable analgesic for acute pain in cancer patients.[1,6] Opioid use in chronic cancer is, however, complex and providers and patients must consider the risks of treatment. Rates of persistent opioid use after curative cancer treatment have been estimated to be between 10.4 to 33.3%, although definitions of persistent use vary between studies.[24,35,36] An additional study showed that cancer survivors had increased rates of chronic opioid use when compared to non-cancer controls, though by 6 years after diagnosis the rates did not differ.[37] Optimally managing cancer patients with opioids requires effective risk stratification methods to identify individuals at higher risk of poor outcomes.[6] Similar to cancer stage informing the management of anti-neoplastic therapy, an accurate prediction of future opioid-related morbidity can be used to personalize pain management and mitigate adverse outcomes. Current guidelines suggest strategies including establishing a signed treatment agreement, periodic urine drug testing, patient and caregiver education, referrals to palliative medicine or a pain specialist, avoidance of high risk formulations and minimizing total daily dose for patients at increased risk of adverse opioid-related outcomes.[6,38–41]

This study identified multiple patient, cancer, and treatment factors statistically significantly associated with risk for persistent opioid use in cancer patients. Cancers with more intensive, multi-modal therapies had the highest adjusted-risk for persistent opioid use including esophagus, pancreas, liver, head-and-neck and lung cancer. Prior opioid use was highly associated with future chronic use. The rate of persistent use was 72.2% among prior chronic users compared to 1.5% of opioid naïve patients that did not receive a prescription during treatment. Our results also support prior research demonstrating increased risk for opioid use among younger patients, the unemployed, current or former smokers and those with a prior diagnosis of depression or drug abuse. [10,26,42–44] Other factors associated with opioid risk identified in this study such as race, median income, non-abusive alcohol use, comorbidity, BMI and cancer type have not been previously reported.[42,45,46] We found no association between gender and persistent opioid use, which differs from other studies,[10,26,28,43] though one must consider the skewed gender distribution of our study population within the VA healthcare system. Many patient, cancer and treatment related factors were consistently predictive of the three opioid-related study endpoints which likely stems from persistent opioid use being a mediator for downstream adverse opioids events.

The data-driven predictive models developed in this project differ from existing opioid risk prediction tools. The Opioid Risk Tool represents a commonly used screening tool developed by expert opinion to predict aberrant behavior in non-cancer patients. [10] Select risk factors for persistent use in our models agreed with predictors used in the Opioid Risk Tool including age, history of drug or alcohol abuse, and depression. In contrast with the Opioid Risk Tool, having a high risk psychiatric condition (ADD, OCD or Schizophrenia) in our predictive

model was not associated with increased adjusted risk for persistent use among cancer survivors, which could be a response to more rigid monitoring or prevention strategies in these patients. Additional screening tools include the Screener and Opioid Assessment for Patients with Pain-Revised (SOAPP), its revised edition (SOAPP-R), the Brief Risk Questionnaire (BRQ) and the current opioid misuse measure (COMM) – all of which are self-reported questionnaires that assess psychologic and behavior patterns identified by experts to be associated with opioid misuse.[11,47–49] It should be noted that all of these previously developed tools were explicitly developed and validated in non-cancer populations. Additionally, one must consider that the predictive ability of self-reported questionnaires can be limited by their dependence on accurate reporting of potentially incriminating behaviors.[48] The domains covered by the psychometric questionnaires are largely independent of the factors used in this population-based study. These inherent differences make direct comparisons between risk prediction models difficult, however one could hypothesize that the two approaches may be complimentary.

This study has several limitations worth considering. Most notably, one must consider whether the results from a cohort of predominantly male military veterans will generalize to a non-military population. In addition to gender differences, veterans are more likely to have health insurance coverage and less likely to live below the poverty line when compared to the general population.[50] Furthermore, combat veterans have higher rates of exposure to mental and physical trauma that could increase their risk for substance abuse or dependence.[51] Validation in a non-VA cohort of cancer patients is required to help understand generalizability of our findings and determine the predictive ability for the general population.

The retrospective nature of this analysis raises questions surrounding the accuracy of ascertaining opioid use, abuse, or dependence from electronic health records. Our observed rates of adverse opioid-related events were similar to other studies[24,26,36,52,53] , though overall these events may be under-reported in cancer patients, especially when using claims-based data.[52] It is also possible that there was a misclassification of recurrence status and that some patients included in this cohort had disease progression and underwent additional salvage therapy. The observational population-based nature of this study also precludes the ability to evaluate known predictive factors such as prior trauma, family history or focused patient-directed questions that have been previously shown to be associated with opioid abuse.[10,12,13] The primary endpoint of persistent opioid use is limited to opioid prescriptions prescribed within the VA system. There are also limitations in our definition of opioid abuse or dependence, which typically requires the observation a problematic pattern of opioid use leading to clinical impairment or distress.[29]

Despite these limitations, this current study represents one of the largest comprehensive evaluations of persistent opioid use and abuse in cancer survivors, and the first to construct a predictive model in oncology patients.[24,35,43] The absolute rate of persistent opioid use, abuse and dependence was relatively low among this cohort of cancer survivors, especially among those without prior opioid use. Improved risk stratification will allow for personalized risk assessment and improve the safety of pain management in cancer survivors. Future work is needed to externally validate these models, ideally in a prospective setting.

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Notes

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TABLES

Table 1. Patient, cancer and treatment characteristics of patients stratified by the primary outcome of persistent opioid 1 year after treatment*

Covariate	**No Persistent Opioid Use** (n=97,923)	**Persistent Opioid Use** (n=8,808)
Age (mean (SD))	65.02 (8.59)	62.07 (8.05)
Male (%)	94850 (96.9)	8400 (95.4)
Race (%)		
Black	22076 (22.5)	1712 (19.4)
Other	2770 (2.8)	221 (2.5)
White	73077 (74.6)	6875 (78.1)
Employed (%)	12145 (12.4)	651 (7.4)
Married (%)	49416 (50.5)	3971 (45.1)
Zip Code Metrics		
Rural (%)	26211 (26.8)	2355 (26.8)
% with HS Diploma (mean (SD))	85.6 (8.3)	85.7 (7.8)
Median Income (mean $10k (SD))	50.1 (1.85)	48.9 (1.69)
Tobacco Use (%)		
Current	30143 (30.8)	4054 (46.0)
Never	20531 (21.0)	1083 (12.3)
Past	32940 (33.6)	2595 (29.5)
Unknown	14309 (14.6)	1076 (12.2)
Alcohol Use (%)		
Current	37476 (38.3)	3211 (36.5)
None	29975 (30.6)	2472 (28.1)
Past	16049 (16.4)	2030 (23.0)
Unknown	14423 (14.7)	1095 (12.4)
BMI (%)		
Healthy Weight	25932 (27.4)	2638 (30.8)
Overweight	64845 (68.6)	5302 (61.9)
Underweight	3704 (3.9)	623 (7.3)
Prior Diagnoses		
Alcohol Abuse (%)	14959 (15.3)	2473 (28.1)
Depression (%)	19202 (19.6)	3566 (40.5)
High Risk Psychiatric Condition (%)	5078 (5.2)	776 (8.8)
Non-Opioid Drug Abuse (%)	6810 (7.0)	1407 (16.0)
Opioid Abuse (%)	1384 (1.4)	558 (6.3)
CCI (%)		

0	41292 (42.2)	2857 (32.4)
1	18793 (19.2)	1845 (20.9)
2	17342 (17.7)	1552 (17.6)
3+	20496 (20.9)	2554 (29.0)
Prior Opioid Use (%)		
Opioid Naïve-New Prescription	33383 (34.1)	2216 (25.2)
Opioid Naïve-No Prescription	50115 (51.2)	779 (8.8)
Prior Chronic Use	1354 (1.4)	3509 (39.8)
Prior Intermittent Use	13071 (13.3)	2304 (26.2)
Primary Cancer (%)		
Bladder	4946 (5.1)	434 (4.9)
Breast	2456 (2.5)	270 (3.1)
Colon	10007 (10.2)	630 (7.2)
Esophagus	806 (0.8)	164 (1.9)
Gastric	586 (0.6)	79 (0.9)
Head and Neck	9315 (9.5)	1701 (19.3)
Kidney	7142 (7.3)	842 (9.6)
Liver	739 (0.8)	182 (2.1)
Lung	8132 (8.3)	1409 (16.0)
Pancreas	251 (0.3)	44 (0.5)
Prostate	51361 (52.5)	2894 (32.9)
Rectum	2182 (2.2)	159 (1.8)
AJCC 7th ed. Stage (%)		
I	30206 (30.8)	3226 (36.6)
II	52384 (53.5)	3531 (40.1)
III	11026 (11.3)	1216 (13.8)
IV	4307 (4.4)	835 (9.5)
Local Treatment (%)		
RT	36160 (36.9)	3118 (35.4)
Surgery	57255 (58.5)	5017 (57.0)
Surgery + RT	4508 (4.6)	673 (7.6)
Chemotherapy (%)	8416 (8.6)	1534 (17.4)

*The groups significantly differed for all covariates ($p < 0.01$) except for rural status and rates of high school graduation. P values were calculated with a two-sided Chi-squared test for categorical variables and a two-sided t-test for continuous variables.

Abbreviations: SD, Standard Deviation; HS, High School; BMI, Body Mass Index; CCI, Charlson Comorbidity Index; AJCC, American Joint Committee on Cancer; ed., edition; RT, Radiation Therapy.

Table 2. LASSO logistic regression predictive model covariates by outcome*

Variable	Chronic opioid use	Opioid abuse	Opioid toxicity
Intercept	-2.670	-2.833	-3.966
Age (per 10 years)	-	-0.018	-0.002
Depression	0.109	-	0.026
Alcohol Abuse	-	0.018	-
Non-Opioid Drug Abuse	-	1.095	0.625
Past Opioid Drug Abuse	-	2.616	2.186
Prior opioid use			
Opioid-naïve – New Prescription (REF)	-	-	-
Opioid-Naïve – No Prescription	-0.726	-	-0.045
Prior Chronic Use	3.209	-	-
Prior Intermittent Use	0.554	-	-
Chemotherapy	0.078	0.877	0.677

Abbreviations: LASSO, least absolute shrinkage and selection operator; RT, radiation therapy; AJCC 7, American Joint Committee on Cancer staging system 7th edition; REF, reference group.

*Table of log odds covariates from final predictive models, omitting covariates not predictive in any model. Cell color gradients with red = increasing probability of an opioid event, and blue decreasing probability of an opioid event.

Figure Titles and Legends

Figure 1. Rates of adverse opioid events among cancer survivors. Rates of persistent opioid use (top), new diagnosis of opioid abuse or dependence (middle) and admission for opioid abuse, dependence or toxicity (bottom) by cancer type. Abbreviations: HNC, Head and Neck Cancer.

Figure 2. Association of covariates with adverse opioid events. Forest plot showing multivariable adjusted odds ratios of covariates for persistent opioid use (left), a future diagnosis of opioid abuse or dependence (middle) or in-patient admission related to opioid toxicity (right). Error bars represent 95% confidence intervals. † Not to scale, OR = 35.42 (32.71-38.36); ‡ Not to scale, OR = 13.52 (11.99-15.25); *Not to scale OR = 7.22 (6.29-8.28). Abbreviation: *ref* = reference category.

Figure 3. Validation of parsimonious model. A) ROC curve showing discrimination of LASSO model in predicting persistent opioid use, a future diagnosis of opioid abuse or dependence and future admissions for opioid abuse, dependence or toxicity. B) Bar plot showing incidence of persistent opioid use for the predicted risk groups.

Figure 1

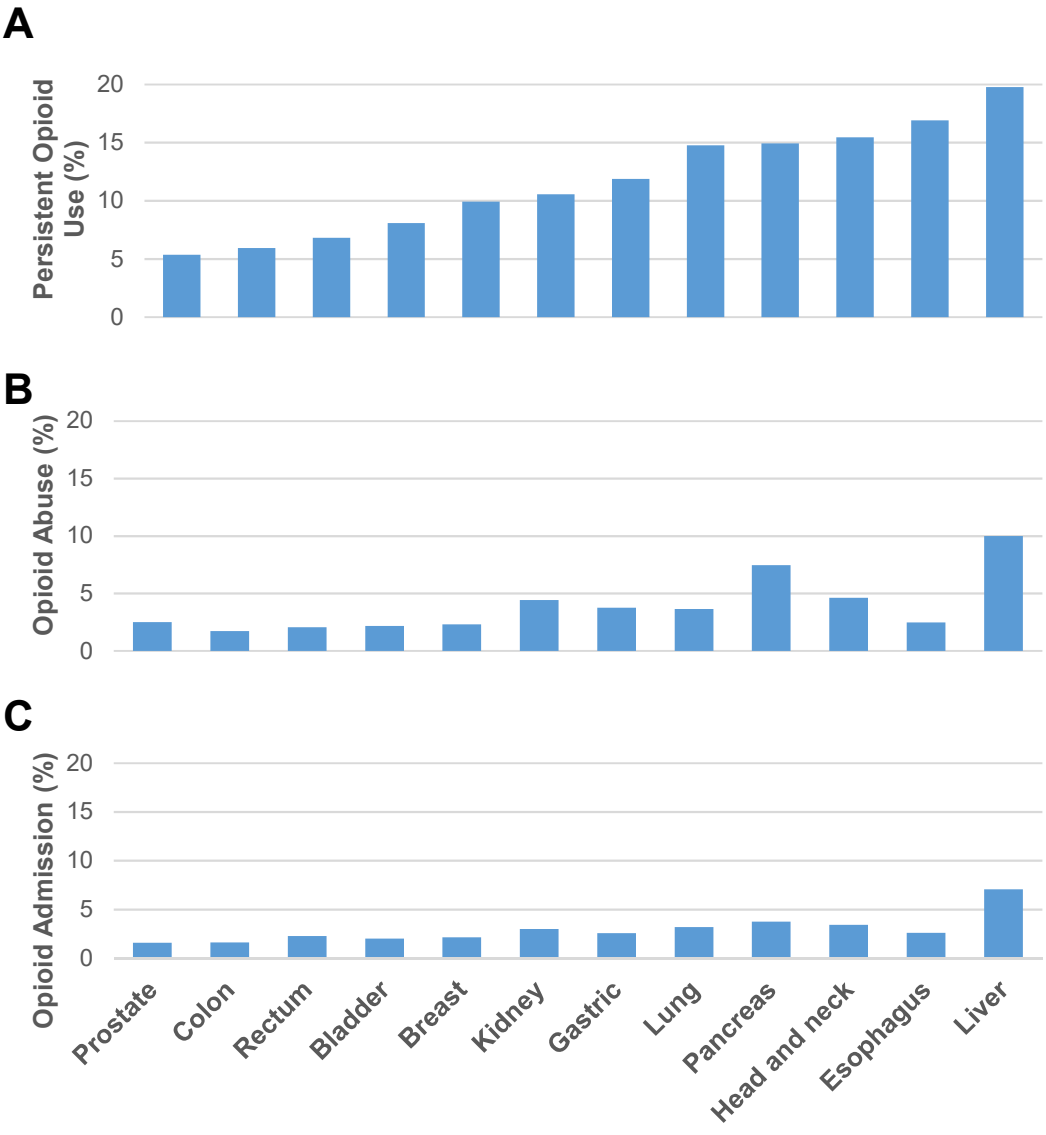

Figure 1

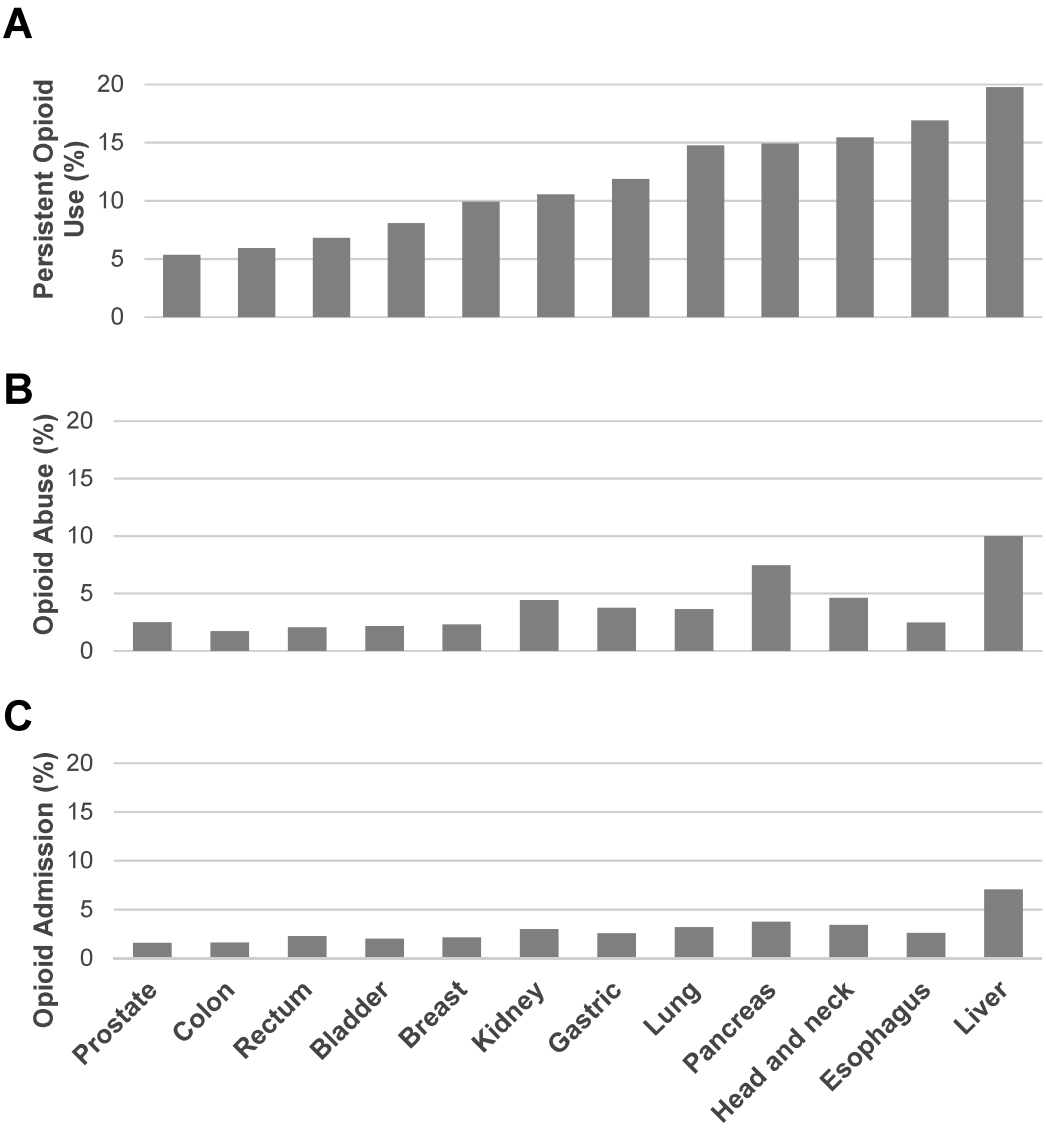

Figure 2

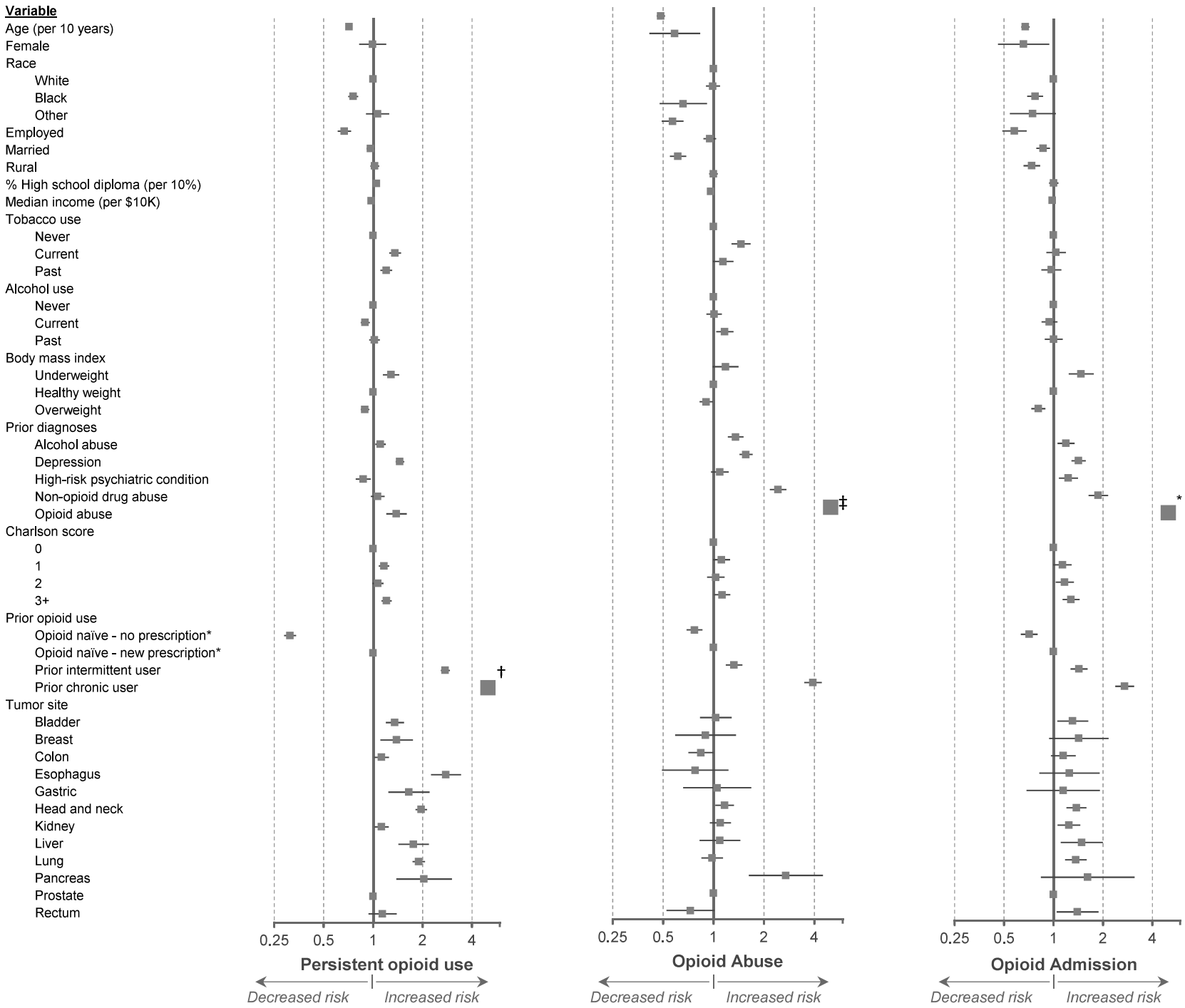

Figure 2_color--FINAL

Figure 2

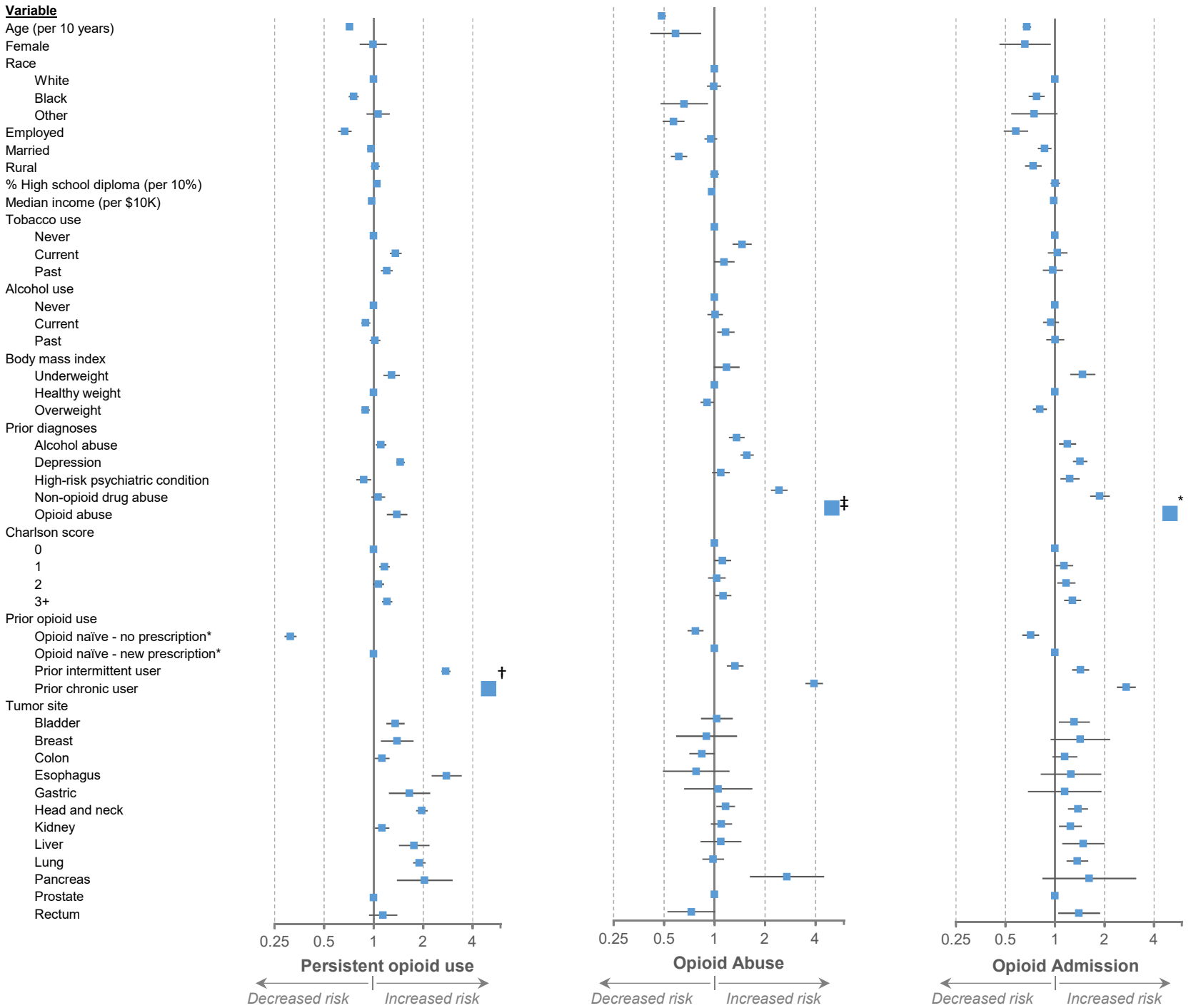

Figure 3