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# A Novel Risk Prediction Model for Checkpoint Inhibitor-Related Autoimmune Toxicities

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**14. ABSTRACT**

Recent research has shown the effectiveness of immunotherapy treatments in managing patients with both incurable and curable cancers. These immune checkpoint inhibitor treatments turn the patient's immune system against cancer cells, resulting in impressive and long-lived responses to cancer treatment in many patients. While incredibly effective for some, these treatments do not work for all patients and they are unfortunately associated with toxicities arising from the immune system attacking the patient's own body. So-called autoimmune toxicities can range from mild and self-limited, to severe and life threatening. The research reviewed here examines predictive features of these autoimmune toxicities. The goal is the development of a risk prediction model for autoimmune toxicities from cancer immunotherapy, with secondary goals examining the impact on survival from these immunotherapy induced autoimmune events and predictors of overall survival among cancer patients receiving immunotherapy.

**15. SUBJECT TERMS**

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## 1. Introduction:

Immune checkpoint inhibitors (ICI) have revolutionized cancer therapy over the past decade. With extensive Federal Drug Administration (FDA) approvals in numerous cancer diagnoses, the impact of these therapies has been substantial. While effective and safe for some patients, the majority of those treated will not respond to ICI therapy, and therapy can be associated with substantial and life-changing autoimmune toxicities. The risk of treatment related autoimmune toxicities is currently described by clinical trials that were underpowered to detect their true incidence, and limited knowledge is known about relative risks of these toxicities among patients starting immunotherapy treatments. Additional knowledge of the risks of these autoimmune complications is needed, and validated tools to predict risks for an individual patient are crucial to ongoing counseling and treatment of individual patients. This grant's goal is to develop a risk prediction model for autoimmune toxicities related to ICI among cancer patients. Additional goals aim to better understand the impact of autoimmune toxicities on survival in cancer patients receiving ICI as well as better describe real-world rates of toxicities.

**Objective:** The objective of the proposed research is the development of a validated risk prediction tool for checkpoint inhibitor related autoimmune toxicities.

***Specific Aims:***

**Aim 1** – To describe rates of autoimmune toxicities within a real-world patient dataset across multiple tumor types. We will utilize a large patient dataset from the VHA and WUSTL to describe observed rates of irAEs amongst patients receiving checkpoint inhibitors.

**Aim 2** – To develop a risk prediction model for grade 3-4 immune related adverse events in patients receiving immunotherapy. We plan to utilize a large patient database from the VHA and WUSTL to develop a prediction model for immunotherapy toxicities.

**Aim 3** – To assess the association between grade 3-4 immune related adverse events and clinical outcomes in patients receiving immunotherapy. We will conduct analyses of immune checkpoint inhibitor toxicity and its impact on PFS and OS amongst cancer patients treated with immune checkpoint inhibitors.

***Study Design:*** This is a retrospective cohort study that is utilizing a large patient dataset of ICI recipients through the Veteran Affairs Health Administration and a second data set from Washington University in St. Louis. Rates of ICI toxicities are being assessed utilizing both datasets, and legacy as well as machine learning techniques will be utilized to determine the optimal risk prediction model for the development of autoimmune toxicities.

***Impact:*** The research proposed is innovative and important for several reasons. (1) It will provide vital information about rates of ICI toxicities in a racially and economically diverse population. (2) It will develop and validate a crucial risk prediction tool that will help inform patients and physicians as to the relative risks of ICI related autoimmune toxicities. (3) It will investigate the relationships between toxicities and outcomes amongst ICI recipients, an evolving area of research. These findings will directly inform and impact patient care in an immediate manner, improving the management and outcomes of many cancer patients

## 2. Keywords

***Immunotherapy, Cancer, Autoimmune, Immune related adverse events, Checkpoint inhibitors, Oncology, Immunology, Outcomes Research, Machine Learning, Regression analysis.***

## 3. Accomplishments

**We have had ongoing accomplishments on the research project and several ongoing difficulties/obstacles with some personnel issues that limited productivity over the course of the 2022-2023 funding period. Interesting findings on the impact of time of therapy administration have opened up new areas of interest in the research endeavor, and are currently being incorporated into a proposal for a randomized clinical trial within the VA environment for which independent funding is being sought. We have completed an initial publication of our findings from pneumonitis (publication enclosed). Publications on timing of immunotherapy and frailty score evaluations and OS in ICI therapy are seeking publication. Personnel issues with statistician support and chart abstraction have held up the study and a no cost extension was granted to provide additional time to complete final analyses and write-up of grant efforts. We will review status of the ongoing project and next steps as outlined below.**

**MAJOR TASK 1:** *Regulatory Approval and Credentialing*

*Task Overview:* All necessary regulatory approvals have been obtained. Annual reviews have proceeded without issues.

- ***Subtask 1: IRB Approvals at WUSTL and STLVAMC***
    - This has been completed prior, all approvals obtained/established by August 2020
- ***Subtask 2: VA WoC Appointments for WUSTL collaborators***
    - This has been completed for key investigators, and for a collaborating team of chart abstractors (Washington University Resident Physicians). However, some team members have not necessitated a without compensation appointment at the St. Louis VA Medical Center (Inez Oh, PhD and Randi Foraker, PhD).
- ***Subtask 3: Data sharing arrangements for WUSTL and STLVAMC***
    - The sharing of data at this time in the grant is not necessary and we have pushed forward with alternate aims of the grant. Potential workarounds for this component of the grant have been developed (model sharing instead of data sharing).
- ***Subtask 4: Coordinate with sites for annual IRB approval, continuing review annually***
    - Subsequent annual reviews have been approved at the St. Louis VA Medical Center.
    - Washington University in St. Louis subsequent annual review is approved.
- ***Subtask 5: HRPO review/approval of IRB protocols***
    - HRPO approval reviews completed at all sites and DOD.

**MAJOR TASK 2:** *Analysis of VA and WUSTL data to obtain rates of autoimmune toxicities*.

*Task Overview:* The analysis of the dual datasets at the St. Louis Veterans Affairs Medical Center and Washington University is ongoing. Several key tasks have already been completed. The initial plan to utilize ICD Codes to identify toxicities has been employed with success, however a publication released at the beginning of the funding period raised potential complications to this approach. In an article entitled *Comparative assessment of manual chart review and ICD claims data in evaluating*

*immunotherapy-related adverse events* by *Nashed, Zhang, et al*, a curated list of ICD codes was found to be ineffective at capturing autoimmune toxicity events among cancer patients receiving immunotherapy. As such, the abstraction of charts has become a significantly more important component of the study. This has added additional time, and has delayed some components of the tasks. **At the present time we have been successful at identifying Prednisone prescription as a highly sensitive and reasonably specific mechanism of identifying autoimmune toxicities among patients with Melanoma. We plan to continue this approach of abstraction and have completed Head and Neck SCC and GU malignancies, Lung is ongoing.**

### *Subtask 1: Identify ICD9/10 codes for autoimmune toxicities of interest*

- Based off a study through Ohio State University and our own analysis, we have identified a comprehensive list of candidate ICD codes for autoimmune toxicities of interest. These are all listed below via table form, within Table 1, 2 and 3:

**Table 1: Pneumonitis/Pulmonary Autoimmune ICD Toxicity Codes**

| Pneumonitis Diagnosis | ICD10 | ICD9 | Pneumonitis Diagnosis | ICD10 | ICD9 | Pneumonitis Diagnosis | ICD10 | ICD9 |
|---|---|---|---|---|---|---|---|---|
| Drug induced pneumonitis | J70.4 | 508.8 | Dyspnea | R06.2 | 786.07 | Chronic respiratory failure, with hypercapnia | J96.12 | 518.8 |
| Acute drug-induced interstitial lung disorders | J70.2 | 508.8 | Chest pain on breathing | R07.1 | 786.52 | Acute and chronic respiratory failure, unspecified whether with hypoxia or hypercapnia | J96.20 | 518.5 |
| Pneumonitis due to inhalation of other solids and liquids | J69.8 | 507.8 | Acute respiratory failure, unspecified whether with hypoxia or hypercapnia | J96.00 | 518.51 | Acute and chronic respiratory failure, unspecified whether with hypoxia or hypercapnia | J96.20 | 518.8 |
| Cough | R05 | 786.2 | Acute respiratory failure, unspecified whether with hypoxia or hypercapnia | J96.00 | 518.81 | Acute and chronic respiratory failure, with hypoxia | J96.21 | 518.5 |
| Dyspnea, unspecified | R06.00 | 786.1 | Acute respiratory failure, with hypoxia | J96.01 | 518.51 | Acute and chronic respiratory failure, with hypoxia | J96.21 | 518.8 |
| Orthopnea | R06.01 | 786 | Acute respiratory failure, with hypoxia | J96.01 | 518.81 | Acute and chronic respiratory failure, with hypercapnia | J96.22 | 518.5 |
| Shortness of breath | R06.02 | 786.1 | Acute respiratory failure, with hypercapnia | J96.02 | 518.51 | Acute and chronic respiratory failure, with hypercapnia | J96.22 | 518.8 |
| Acute respiratory distress | R06.03 | 518.8 | Acute respiratory failure, with hypercapnia | J96.02 | 518.81 | Respiratory failure, unspecified, unspecified whether with hypoxia or hypercapnia | J96.90 | 518.8 |
| Acute respiratory distress | R06.03 | 770.9 | Chronic respiratory failure, unspecified whether with hypoxia or hypercapnia | J96.10 | 518.83 | Respiratory failure, unspecified, with hypoxia | J96.91 | 518.8 |
| Other forms of dyspnea | R06.09 | 786.1 | Chronic respiratory failure, with hypoxia | J96.11 | 518.83 | Respiratory failure, unspecified, with hypercapnia | J96.92 | 518.8 |

**Table 2: Hepatic Autoimmune ICD Toxicity Codes**

| Hepatitis Realated Diagnosis | ICD10 | ICD9 | Hepatitis Related Diagnosis | ICD10 | ICD9 |
|---|---|---|---|---|---|
| Autoimmune hepatitis | K75.4 | 571.42 | Hepatic sclerosis | K74.1 | 571.9 |
| Nonspecific reactive hepatitis | K75.2 | 573.3 | Hepatic fibrosis with hepatic sclerosis | K74.2 | 571.9 |
| Other chronic hepatitis, not elsewhere classified | K73.8 | 571.49 | Primary biliary cirrhosis | K74.3 | 571.6 |
| Hepatic failure, unspecified with coma | K72.91 | 572.2 | Secondary biliary cirrhosis | K74.4 | 571.6 |
| Hepatic failure, unspecified with coma | K72.91 | 572.8 | Biliary cirrhosis, unspecified | K74.5 | 571.6 |
| Hepatic failure, unspecified without coma | K72.90 | 572.8 | Unspecified cirrhosis of liver | K74.60 | 571.5 |
| Acute and subacute hepatic failure without coma | K72.00 | 570 | Other cirrhosis of liver | K74.69 | 571.5 |
| Acute and subacute hepatic failure with coma | K72.01 | 570 | Toxic liver disease with hepatic necrosis, without coma | K71.10 | 573.3 |
| Acute and subacute hepatic failure with coma | K72.01 | 572.2 | Toxic liver disease with hepatic necrosis, with coma | K71.11 | 572.2 |
| Inflammatory liver disease, unspecified | K75.9 | 573.3 | Toxic liver disease with hepatic necrosis, with coma | K71.11 | 573.3 |
| Toxic liver disease with acute hepatitis | K71.2 | 573.3 | Nonspecific elevation of levels of transaminase and lactic acid dehydrogenase | R74.0 | 790.4 |
| Liver disorders in diseases classified elsewhere | K77 | 573.8 | Obstruction of bile duct | K83.1 | 576.2 |
| Hepatic fibrosis | K74.0 | 571.5 | Disorder of bilirubin metabolism, unspecified | E80.7 | 277.4 |

**Table 3: GI Autoimmune ICD Toxicity Codes**

| Colitis | ICD10 | ICD9 | Colitis | ICD10 | ICD9 |
|---|---|---|---|---|---|
| Toxic gastroenteritis and colitis | K52.1 | 558.2 | Eosinophilic gastritis or gastroenteritis | K52.81 | 535.71 |
| Other specified noninfective gastroenteritis and colitis | K52.89 | 558.9 | Eosinophilic gastritis or gastroenteritis | K52.81 | 558.41 |
| Other specified noninfective gastroenteritis and colitis | K52.89 | 787.91 | Eosinophilic colitis | K52.82 | 558.42 |
| Indeterminate colitis | K52.3 | 558.9 | Collagenous colitis | K52.831 | 558.9 |
| Gastroenteritis and colitis due to radiation | K52.0 | 558.1 | Lymphocytic colitis | K52.832 | 558.9 |
| Toxic gastroenteritis and colitis | K52.1 | 558.2 | Other microscopic colitis | K52.838 | 558.9 |
| Food protein-induced enterocolitis syndrome | K52.21 | 558.3 | Microscopic colitis, unspecified | K52.839 | 558.9 |
| Food protein-induced enteropathy | K52.22 | 558.3 | Noninfective gastroenteritis and colitis, unspecified | K52.9 | 558.9 |
| Other allergic and dietetic gastroenteritis and colitis | K52.29 | 558.3 | Diarrhea | R19.7 | 787.91 |
| Other allergic and dietetic gastroenteritis and colitis | K52.29 | 787.91 | Unspecified abdominal pain | R10.9 | 789 |
| Eosinophilic gastritis or gastroenteritis | K52.81 | 535.7 | Melena, blood in stool | K92.1 | 578.1 |
| Mucus in stool | R19.5 | 787.7 | | | |

## *Subtask 2: Evaluate pharmacy data to identify patients receiving steroids*

- We have identified within both our Veterans Affairs Dataset and the Washington University in St. Louis dataset those patients receiving an outpatient prescription of Prednisone (steroid-therapy) following an initial dose of a checkpoint inhibitor up to 6 months after their final dose of a checkpoint inhibitor. These numbers and details are presented below:

**Table 4: Checkpoint inhibitor administered and Number of patients receiving prednisone in Washington University Dataset**

| Medication Administered | Number of Patients | Patients Receiving Prednisone |
|---|---|---|
| Pembrolizumab | 695 | 82 |
| Nivolumab | 1078 | 157 |
| Ipilimumab | 333 | 79 |
| Totals: | 2106 | 318 |

**Table 5: Patient Diagnosis, Drug Therapy and Toxicity Identification by ICD Code and Prednisone Prescription from VA**

| Diagnosis | Number of Patients | Toxicity by ICD Code | Toxicity By Prednisone Prescription |
|---|---|---|---|
| Esophageal Cancer | 65 | 17 | 14 |
| Trachea/Bronchus/Lung | 1991 | 499 | 510 |
| Stomach/Gastric | 30 | 13 | 4 |
| Head and Neck Cancer | 364 | 97 | 58 |
| Colon Cancer/Rectal CA | 79 | 26 | 15 |
| Liver Cancer | 219 | 70 | 41 |
| Bladder Cancer | 364 | 136 | 75 |
| Kidney Cancer | 286 | 87 | 80 |
| Melanoma | 399 | 106 | 99 |
| Breast Cancer | 0 | 0 | 0 |
| Neuroendocrine | 46 | 10 | 5 |
| Hodgkin Lymphoma | 8 | 4 | 4 |
| | | | |
| **Immunotherapy Drugs** | | | |
| Pembrolizumab | 2140 | 418 | 434 |
| Ipilimumab | 265 | 59 | 79 |
| Atezolizumab | 396 | 65 | 79 |
| Nivolumab | 1867 | 464 | 419 |
| Durvalumab | 335 | 49 | 91 |
| Cemiplimab | 18 | 2 | 3 |
| Avelumab | 3 | 0 | 0 |

**Table 6: Patient Diagnosis, Toxicity Identification by ICD Code from VA**

VA RESULTS: ICD Codes to ID Toxicities By Disease of Diagnosis

| Diagnosis | Number of Patients | Colitis | Regional Enteritis | Hepatitis | Renal Toxicity | Pneumonitis |
|---|---|---|---|---|---|---|
| Esophageal Cancer | 65 | 9 | 0 | 0 | 8 | 7 |
| Trachea/Bronchus/Lung | 1991 | 190 | 2 | 25 | 253 | 155 |
| Stomach/Gastric | 30 | 6 | 0 | 1 | 1 | 3 |
| Head and Neck Cancer | 364 | 37 | 0 | 2 | 48 | 38 |
| Colon Cancer/Rectal CA | 79 | 14 | 1 | 1 | 15 | 4 |
| Liver Cancer | 219 | 26 | 0 | 8 | 44 | 7 |
| Bladder Cancer | 364 | 42 | 1 | 6 | 101 | 22 |
| Kidney Cancer | 286 | 35 | 3 | 7 | 56 | 13 |
| Melanoma | 399 | 45 | 2 | 5 | 55 | 14 |
| Breast Cancer | 0 | 0 | 0 | 0 | 0 | 0 |
| Neuroendocrine | 46 | 6 | 0 | 0 | 8 | 1 |
| Hodgkin Lymphoma | 8 | 1 | 0 | 0 | 3 | 1 |
| Total: | 3851 | | | | | |

**Table 7: Patient Diagnosis, Toxicity Identification by ICD Code from Washington University**

| Cancer Type | Number of Patients Receving Prednisone |
|---|---|
| Neuroendocrine | 9 |
| Lung | 91 |
| Esophageal | 8 |
| Stomach | 5 |
| Head and Neck | 33 |
| Kidney | 21 |
| Liver | 11 |
| Melanoma | 72 |
| Colorectal | 19 |
| Hodgkin Lymphoma | 9 |
| Breast | 19 |
| Bladder | 6 |

These results are outlined in Tables 4, 5, 6 and 7. Table 4 provides a brief overview of varieties of checkpoint inhibitor administered and the numbers of patients within each group receiving prednisone (potential autoimmune toxicities) within the Washington University dataset. Table 5 outlines patient diagnosis, drug treatment and toxicity identification with ICD codes and Prednisone prescription from the VA. Table 6 outlines (using VA data) the indicence of particular toxicities by disease state. Table 7 shows the close correlation of ICD code toxicities with Prednisone prescriptions from Washington University.

Given the unreliable correlation of ICD codes with the occurrence of real irAEs, we have aimed to confirm that the outpatient prescription of a certain dose of Prednisone is correlated with a real autoimmune toxicity. We have, **over the last calendar year, we have completed the abstraction of patients from the Genitourinary and Head and Neck squamous cell cancer cohorts. Direct abstraction is extremely time-consuming and has taken longer than anticipated. Due to time commitments involved, we have spent substantial efforts on novel findings noted as parts of the ancillary analyses. A no-cost extension has been granted to continue to wrap up efforts around abstraction and final analysis.** Overall, to date, we have found that Prednisone prescription is a very reliable mechanism of identification of immune related autoimmune toxicities and is associated with a 100% sensitivity and a 76% specificity for the detection of autoimmune events in our Melanoma cohort. The gross numbers are outlined below in Table 8 and test characteristics are seen in Table 9. Removing patients with steroids prescribed for brain metastases resulted in a much improved specificity (88%) and PPV (0.79). This is outlined in Table 9 and 10 below. This finding provides an approach to identify cases of irAEs administratively. **We are in the process of seeking publication of this finding.** Furthermore, we hope to apply this to portions of the cohort that may be difficult to finish abstracting given time remaining on the grant and personnel issues.

**Table 8: Prednisone Prescription for Identification of irAE: Gross Numbers from Abstracted VA Cohort**

| Prednisone And irAEs | Positive for irAE | Negative for irAE | Total |
|---|---|---|---|
| **Positive Prednisone Prescription** | 97 | 63 | 160 |
| **Negative Prednisone Prescription** | 0 | 196 | 196 |
| **Totals** | 97 | 259 | |

**Table 9: Prednisone Prescription for Identification of irAEs: Test Characteristics**

| | |
|---|---|
| True Positives | 97 |
| True Negatives | 196 |
| False Positive | 63 |
| False Negatives | 0 |
| Sensitivity | 1 |
| Specificity | 0.757 |
| PPV | 0.61 |
| NPV | 1 |

**Table 10: Prednisone Prescription for Identification of irAE: Steroids for Brain Metastases Removed**

| Prednisone And irAEs | Positive for irAE | Negative for irAE | Total |
|---|---|---|---|
| **Positive Prednisone Prescription** | 97 | 26 | 123 |
| **Negative Prednisone Prescription** | 0 | 196 | 196 |
| **Totals** | 97 | 222 | |

**Table 11: Prednisone Prescription for Identification of irAE: Steroids for Brain Metastases Removed**

| | |
|---|---|
| True Positives | 97 |
| True Negatives | 196 |
| False Positive | 26 |
| False Negatives | 0 |
| Sensitivity | 1 |
| Specificity | 0.88 |
| PPV | 0.79 |
| NPV | 1 |

## *Subtask 3: Comparison of patients identified in ST1 with ST2 4-7*

- We have performed analyses within the Veterans Affairs population of the clinical/demographic characteristics of patients who have received prednisone versus those that have not. Initial analyses of patient characteristics, including rates of comorbidities, sex, age, and tumor type are described below in Table 12.

**Table 12: Patient Diagnosis, Toxicity Identification by ICD Code from VA**

| Demographic clinical characteristics | Total (N=2,841) | | P-value |
|---|---|---|---|
| | Prednisone Yes n=361 | Prednisone No n=2,480 | |
| Age (mean years, range) | 68.7 (71) | 68.7 (68) | 0.20† |
| Male (%) | 95.6 | 96.9 | 0.19* |
| Charlson score index (mean) | 4.6 | 4.5 | 0.68† |
| Cancer type (%) | | | 0.02* |
| Bladder | 6.4 | 8.1 | |
| Colon/Rectal | 0.8 | 1.1 | |
| Esophageal | 1.7 | 1.2 | |
| Head and Neck | 3.6 | 8.5 | |
| Hodgkin Lymphoma | 0.6 | 0.2 | |
| Kidney | 9.4 | 5.9 | |
| Liver | 5.5 | 5.4 | |
| Melanoma | 12.7 | 11.5 | |
| Neuroendocrin | 0.6 | 0.7 | |
| Stomach | 0.3 | 0.7 | |
| Trachea/Bronchus/Lung | 58.5 | 56.9 | |

* Chi-square test

† T-test

- ***Subtask 4: Abstraction of charts to confirm toxicities found in ST1&ST2***
  - **Abstraction has continued to be very time consuming. We have additionally had some difficulties with abstraction staff turnover. As noted in prior year reports, the onboarding of an abstractor team has been somewhat hampered by excess clinical responsibilities during the COVID-19 pandemic as residents had less free time than anticipated during the planning and design stages of the project. Additionally there has been attrition in the abstractor team members. We are working to improve this. Accomplishments to date include:**
    - **Complete abstraction of Melanoma sub-cohort**
    - **Complete abstraction of Durvalumab (a checkpoint inhibitor) sub-cohort**
    - **Complete abstraction of Head and Neck and GU (Bladder/Renal) cohorts**
    - **Ongoing abstraction of Lung cohort**
  - **At this time, we have achieved additional funding from Washington University in St. Louis via Resident research grants (Mentors in Medicine) for0 additional abstractors, and have an additional Medical Student involved. We are challenged by abstraction, but have adopted additional strategies to overcome this issue (use of Prednisone prescription as a marker for irAEs), and have additional options should this continue to be a roadblock to progress.**
- ***Subtask 5: Compilation of data and reporting of findings***
  - **This is still ongoing and we are awaiting abstraction results prior to compilation/publication as this will make our findings and conclusions more definitive.**

**However, we are planning to proceed with publication if abstraction is not possible to be completed in a timely manner over the period of our additional no cost extension.**

- ***Subtask 6: Manuscript preparation and publication***

    - **As above, this is still ongoing due to progress on abstraction of charts and adjudication of immunotherapy toxicity events. However, several posters and a recent completed publication have already been produced and are included at the end of the report (see enclosure).**

**MAJOR TASK 3:** *To develop a classic regression based risk prediction model*

*Task Overview:* We have proceeded with the development of a risk prediction model to predict both the development of autoimmune toxicities (model 1) and overall survival (model 2) for cancer patients receiving immunotherapy. We have utilized prednisone prescription to identify patients experiencing autoimmune toxicities (method still pending validation) and have reliable markers of survival based from VA death records. Results are detailed below. Final risk model development is still in progress at this time, but univariate and initial multivariate analyses have been completed. Additional Machine Learning models have been utilized over the past year to help establish predictors of OS and autoimmune toxicities and these are presented below in the appropriate sections.

- ***Subtask 1: Classification of patients with autoimmune toxicity as in Aim 1***

    - As detailed above patients who have developed a presumed autoimmune toxicity event have been identified within the dual datasets at the St. Louis VA and Washington University via two methods: ICD codes and Prednisone prescription. These determinations (outlined above) have been utilized to identify toxicity events.

- ***Subtask 2: Establishment of candidate predictors and covariates for model***

We have examined various candidate predictors for potential autoimmune events as well as overall survival for patients undergoing checkpoint inhibitor therapy for a cancer diagnosis. The key components of the current analyses are included in Table 13. Additional planned assessments include leukocyte subsets (absolute neutrophil count, absolute lymphocyte count and absolute eosinophil count), concurrent medications (statin therapy, hypoglycemic therapy), prior antibiotic history, impact of racial disparities, and geographic details. A particularly detailed sub-analysis of metabolic impacts of autoimmune toxicities and overall survival among those receiving immunotherapy will be pursued. The role of these factors have been established through extensive review of the literature as well as analyses of our own data sources. Many of these analyses have been completed, but some are actively ongoing and details of these will be presented below.

**Table 13: Univariate Predictors Examined for Survival/Toxicity**

| Univariate Predictors Examined |
|---|
| Age |
| Cancer Diagnosis |
| Immunotherapy Drug Received |
| Charlson Comorbidity Index |
| History of Dementia |
| History of Stroke |
| History of Peptic Ulcer Disease |
| History of Connective Tissue Disease |
| History of Myocardial Infarction |
| History of Hemiplegia |
| History of Leukemia or Lymphoma |
| History of Diabetes Mellitus |
| History of Heart Failure |
| History of Peripheral Vascular Disease |
| History of Renal Disease |
| History of HIV Infection |
| History of Liver Disease |
| Albumin Levels |
| Creatinine |
| White Blood Cell Count |
| Hemoglobin |
| Body Mass Index |

- ***Subtask 3: Univariate analysis of candidate predictors in VA dataset***
    - We have performed initial univariate analyses of candidate predictor variables for patients within the Veterans Affairs dataset. Outcomes assessed included associations with prednisone prescription and association with overall survival at 1 and 2 years. An extensive list of candidate predictors was considered as outlined in Table 13. Candidate predictors that were found to have a significant univariate association are presented in Tables 14, 15 and 16. Associations were examined between potential predictors and prednisone prescription (marker of autoimmune toxicity) as well as overall survival at 1 and 2 years.

**Table 14: Univariate Association with Prednisone Prescription**

Univariate Associarteion with Prednisone Prescription

| Variable | OR | 95% CI | P-value |
|---|---|---|---|
| Kidney | 1.404 | 0.968, 2.039 | 0.07 |
| Bladder | 0.657 | 0.431, 1.001 | 0.051 |
| Lung | 1.296 | 1.056, 1.589 | 0.01 |
| Pembrolizumab | 0.821 | 0.669, 1.007 | 0.06 |
| Atezolizumab | 0.627 | 0.394, 0.999 | 0.049 |
| Durvalumab | 1.874 | 1.344, 2.613 | 0.0002 |
| CPD | 1.365 | 1.100, 1.695 | 0.005 |
| albumin<3 | 0.451 | 0.342, 0.596 | <0.0001 |
| 1<=creatinine <1.5 | 1.24 | 1.002, 1.536 | 0.045 |
| 10<=HgB<=13 | 0.77 | 0.618, 0.959 | 0.03 |
| Hgb<10 | 0.366 | 0.267, 0.502 | <0.0001 |
| BMI <18.5 | 0.572 | 0.359, 0.911 | 0.0004 |
| 30<BMI<=35 | 1.699 | 1.268, 2.277 | 0.0003 |

**Table 15: Univariate Association with Overall Survival at 1 Year**

Univariate Analysis for Overall Survival at 1 Year

| Variables | HR | 95% CI | P-Value |
|---|---|---|---|
| Age | 1.01 | 1.002, 1.020 | 0.02 |
| Atezolizumab | 1.38 | 1.15, 1.67 | 0.001 |
| Durvalumab | 0.28 | 0.21, 0.40 | <0.0001 |
| Charlson Score index | 1.02 | 1.01, 1.04 | 0.004 |
| HF | 1.27 | 1.13, 1.43 | <0.0001 |
| CVD | 1.15 | 1.02, 1.29 | 0.03 |
| Hepatic Disease | 1.39 | 1.09, 1.77 | 0.01 |
| Liver disease | 1.2 | 1.07, 1.34 | 0.002 |
| BMI (2841) | | | <0.0001 |
| BMI <18.5 | 1.83 | 1.56, 2.14 | |
| 18.5<=BMI<25 (ref) | | | |
| 25<=BMI<30 | 0.63 | 0.56, 0.72 | |
| BMI>=30 | 0.51 | 0.43, 0.59 | |

**Table 16: Univariate Association with Overall Survival at 2**

Univariate Association with Overall Survival at 2 Years

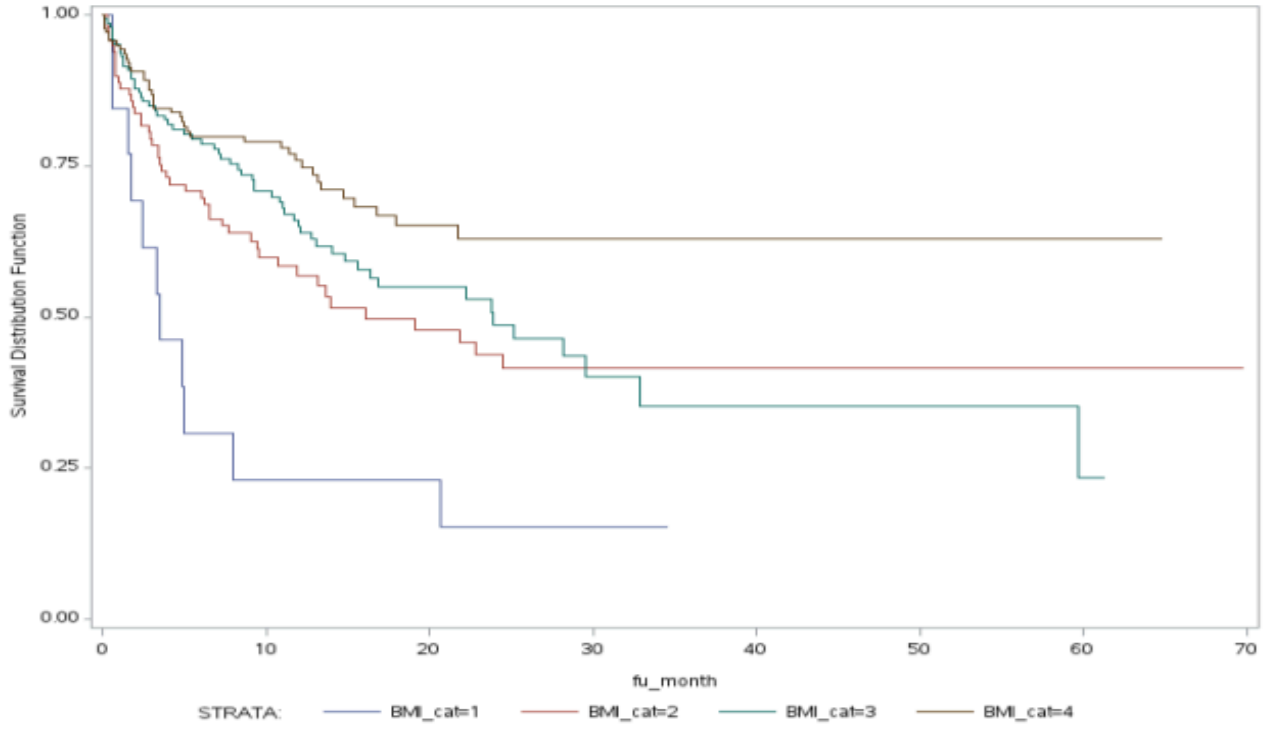
| Variables | HR | 95% CI | P-Value |
|---|---|---|---|
| Esophageal | 2.24 | 1.57, 3.20 | <0.0001 |
| Bladder | 1.29 | 1.10, 1.52 | 0.002 |
| Liver | 1.36 | 1.12, 1.65 | 0.002 |
| Melanoma | 0.54 | 0.46, 0.65 | <0.0001 |
| Durvalumab | 0.33 | 0.25, 0.43 | <0.0001 |
| Charlson Score index | 1.02 | 1.01, 1.04 | 0.003 |
| HF | 1.27 | 1.14, 1.42 | <0.0001 |
| PVD | 1.11 | 1.01, 1.23 | 0.03 |
| CVD | 1.13 | 1.02, 1.26 | 0.03 |
| Hepa | 1.31 | 1.05, 1.65 | 0.02 |
| Liver disease | 1.15 | 1.04, 1.28 | 0.01 |
| 3<=albumin<=3.5 | 2.28 | 2.02, 2.58 | |
| albumin<3 | 6.48 | 5.75, 7.30 | |
| Creatinine (2838) | | | <0.0001 |
| creatinine <1 (ref) | | | |
| 1<=creatinine <1.5 | 0.61 | 0.55, 0.67 | |
| 1.5<=creatinine <2 | 0.62 | 0.52, 0.76 | |
| creatinine >=2 | 1.23 | 1.01, 1.49 | |
| WBC (2839) | | | <0.0001 |
| WBC<12 (ref) | | | |
| WBC>=12 | 3.37 | 3.00, 3.79 | |
| HgB (2776) | | | <0.0001 |
| HgB>13 (ref) | | | |
| 10<=HgB<=13 | 1.84 | 1.62, 2.08 | |
| Hgb<10 | 4.28 | 3.75,4.89 | |
| BMI (2841) | | | <0.0001 |
| BMI <18.5 | 1.75 | 1.50, 2.04 | |
| 18.5<=BMI<25 (ref) | | | |
| 25<=BMI<30 | 0.65 | 0.58, 0.73 | |
| BMI>=30 | 0.55 | 0.48, 0.63 | |

We have undertaken significant assessments of the role of body mass index (BMI) on outcomes for immunotherapy recipients. This has been driven by research supporting the role of BMI as potentially predictive of toxicity events and survival from cancer immunotherapy. Significant findings to date have shown an association with a BMI > 30 (classified as obese) and improved overall survival. These findings are presented below in Figure 1 (Kaplan Meier assessment) and in Table 17 (representing a multivariate model with comorbidities and age as covariates).

**Table 17: Multivariate Association with Overall Survival at 1 year**

| Parameter | Hazard Ratio | 95% Hazard Ratio Confidence Limit |
|---|---|---|
| Obesity (BMI > 30) | 0.402 | 0.200 - 0.809 |
| Romano Comorbidity Score | 1.085 | 0.993 - 1.186 |
| Age | 0.991 | 0.955 - 1.016 |

**Figure 1: Overall Survival Among Immunotherapy Recipients by BMI within VA cohort**



Initial findings from a retrospective analysis of a prospective study became available during the time of this grant's progress that impacted additional analyses. This paper (Qian et al. *Effect of immunotherapy time-of-day infusion on overall survival among patients with advanced melanoma in the USA (MEMOIR): a propensity-score matched analysis of a single-centre, longitudinal study.* Lancet Oncol. 2021 Dec;22 (12) 1777-1786) found that time-of day of checkpoint inhibitor infusion was potentially associated with improved overall survival. This was not an initial potential candidate predictor of overall survival or immunotherapy toxicity that we had considered, but the findings of the paper noted above led us to initiate an initially brief analysis that has opened additional avenues of investigation within the umbrella of this grant. We initially performed univariate analyses of 1 and 2 year OS with time of day and findings are presented below in Table 18 and Table 19**.**

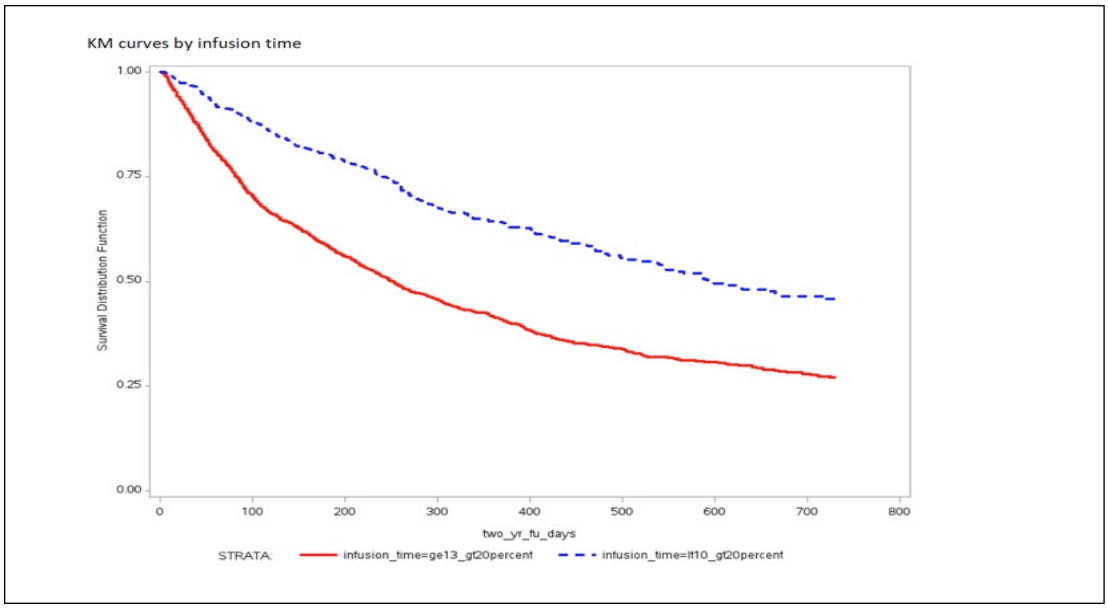
**Table 18: Impact of Early Checkpoint Inhibitor Infusion (Before 10AM) vs Late Infusion (After 1PM) on Overall**

| Disease | 1 Year OS Hazard Ratio | 95% Confidence Interval | P-Value |
|---|---|---|---|
| Lung Cancer (NIVOLUMAB ONLY) | 1.947 | 1.391 - 2.726 | 0.001 |
| Kidney Cancer | 0.951 | 0.489 - 1.848 | 0.8817 |
| Head and Neck Squamous Cell Carcinoma | 2.574 | 1.579 - 4.194 | 0.0001 |
| Bladder Cancer | 2.359 | 1.367 - 4.072 | 0.0021 |
| Melanoma | 5.38 | 1.667 - 17.364 | 0.0049 |

**Table 19: Impact of Early Checkpoint Inhibitor Infusion (Before 10AM) vs Late Infusion (After 1PM) on Overall Survival**

| Disease | 2 Year OS Hazard Ratio | 95% Confidence Interval | P-Value |
|---|---|---|---|
| Lung Cancer (NIVOLUMAB ONLY) | 1.634 | 1.217 - 2.192 | 0.001 |
| Kidney Cancer | 1.119 | 0.621 - 2.017 | 0.7076 |
| Head and Neck Squamous Cell Carcinoma | 2.433 | 1.531 - 3.868 | 0.0002 |
| Bladder Cancer | 2.082 | 1.292 - 3.355 | 0.0026 |
| Melanoma | 3.721 | 1.482 - 9.344 | 0.0051 |

**Figure 2: All Diagnoses, Overall Survival By Infusion Time (BLUE = 50% of infusions before 10AM, RED = 50% of infusions after 1PM**



We additionally performed an exploratory analysis of OS looking at percentage of early (before 10AM) versus late (after 1PM) checkpoint inhibitor infusions, including in this analysis ALL diagnoses. The results of this uncorrected Kaplan Meier analysis is presented in Figure 2 above. Findings of both the univariate analyses by disease state and the general analysis of all diagnoses were significant. This caused us to look deeper into additional analyses looking at time of infusion, including significant interest in whether this impacts toxicities. Concerns about the potential for confounders leading to this observed difference in OS led to additional analyses, including evaluation of the differences in patient characteristics among early versus late treatment recipients and disease specific cohort assessments.

**Table 18: Demographic Data for ALL diagnoses, with > 50% EARLY (<10AM) vs >50% LATE (>1PM) infusion**

Table 18: Demographic Data for ALL patients EARLY vs LATE Treatment

| | Total (N=2544) | | |
|---|---|---|---|
| Demographic clinical characteristics | early treatment n=1729 | late treatment n=815 | P-value |
| Age (mean years) | 68.5 | 68.8 | 0.43† |
| Male (%) | 97.1 | 95.8 | 0.09* |
| Charlson score index (mean) | 4.4 | 4.7 | 0.08† |
| Race (%) | | | 0.08* |
| White | 83.5 | 80.7 | |
| non-whtie | 16.5 | 19.3 | |
| BMI categroy (%) | | | 0.049* |
| BMI<18.5 | 5.5 | 7.9 | |
| 18.5<=Bmi<25 | 41.1 | 43.2 | |
| 25<=Bmi<30 | 30.9 | 29.1 | |
| BMI>30 | 22.5 | 19.8 | |

* Chi-square test

† T-test

The demographic data as above in Table 18 of early versus late treatment showed no significant differences between patient characteristics for early versus late infusion times. As a result of this analysis we looked at Lung cancer as our test case, given it is the largest cohort for analysis. Demographics of early vs late infusion was assessed in Table 19 below. Once again there was little difference in significant features of patients between early and late cohorts. As in Figure 3, uncorrected Kaplan-Meier analyses showed improved OS with early infusion (defined here as < 1PM vs > 1PM). With a goal to control for potential confounders, we performed propensity score matched analyses on the Lung and Melanoma cohort as well as multivariate COX proportional hazards model analysis on these cohorts. These data are presented in Table 20 and 21 below as well as Figures 4 and 5. The ongoing benefit of early infusion with respect to OS was preserved in all of these analyses, including propensity score matching on age and comorbidities.

**Table 19: Demographic features of early vs late treatment in Lung Cancer Cohort**

Table 19: Demographic for lung cancer between early vs. late treatment: LUNG CANCER

| Demographic clinical characteristics | Total (N=1451) | | P-value |
|---|---|---|---|
| | early treatment n=1004 | late treatment n=447 | |
| Age (mean years) | 68.8 | 68.7 | 0.94† |
| Male (%) | 96.1 | 95.5 | 0.60* |
| Charlson score index (mean) | 4.4 | 4.6 | 0.36† |
| Race (%) | | | 0.12* |
| White | 81.2 | 77.6 | |
| non-whtie | 18.8 | 22.4 | |
| BMI categroy (%) | | | 0.13* |
| BMI<18.5 | 4.7 | 7.4 | |
| 18.5<=Bmi<25 | 44.3 | 46.1 | |
| 25<=Bmi<30 | 31.2 | 27.7 | |
| BMI>=30 | 19.8 | 18.8 | |

* Chi-square test

**Figure 3: Kaplan Meier Overall Survival Analysis By Infusion Time (> 50% before 1PM vs > 50% after 1PM): Lung Cancer Cohort**

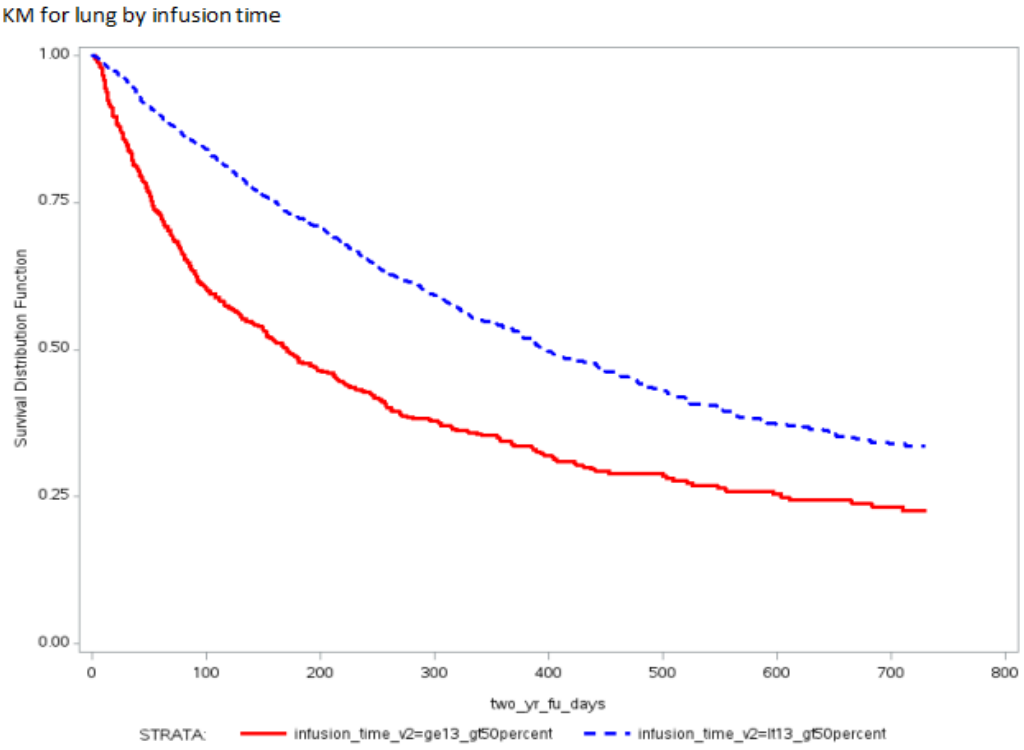


**Table 20: Propensity Score Matched Lung Cohort COX analysis, Controlling for comorbidities, age, BMI, and Race, Two Year**

| Parameter | 2 Year OS Hazard Ratio | 95% Confidence Interval | P-Value |
|---|---|---|---|
| **Infusion Time After 1PM (compared to before 10AM)** | 1.546 | 1.312 - 1.821 | <0.0001 |
| **Age** | 1.01 | 0.999 - 1.021 | 0.0848 |
| **Race (Caucasian vs Non-Caucasian)** | 1.157 | 0.939 - 1.427 | 0.1716 |
| **BMI below 18.5** | 1.294 | 0.944 - 1.776 | 0.1097 |
| **BMI between 25 - 30** | 0.782 | 0.645 - 0.949 | 0.0128 |
| **BMI between 30 - 35** | 0.629 | 0.481 - 0.823 | 0.0007 |
| **BMI greater than 35** | 0.627 | 0.426 - 0.923 | 0.0179 |
| **Romano Comorbidity Score** | 1.043 | 1.015 - 1.071 | 0.0022 |

**Table 21: Demographic features of Early versus Late Infusion Time Among Melanoma Cohort (Propensity Score Matched)**

Table 21: Demographic for melanoma between early vs. late treatment

| Demographic clinical characteristics | Total (N=292) | | P-value |
|---|---|---|---|
| | early treatment n=188 | late treatment n=104 | |
| Age (mean years) | 68.7 | 69 | 0.82† |
| Male (%) | 98.9 | 93.3 | 0.007* |
| Charlson score index (mean) | 3.3 | 3.8 | 0.15† |
| Race (%) | | | 0.01* |
| White | 97.9 | 91.4 | |
| non-whtie | 2.1 | 8.6 | |
| BMI categroy (%) | | | 0.16* |
| BMI<18.5 | 2.1 | 1.9 | |
| 18.5<=Bmi<25 | 23.4 | 35.6 | |
| 25<=Bmi<30 | 36.7 | 32.7 | |
| BMI>=30 | 37.8 | 29.8 | |

* Chi-square test

† T-test

**Table 22: Propensity Score Matched Melanoma Cohort COX analysis, Controlling for comorbidities, age, BMI, and Race, Two Year OS**

| Parameter | 2 Year OS Hazard Ratio | 95% Confidence Interval | P-Value |
|---|---|---|---|
| **Infusion Time After 1PM (compared to before 10AM)** | 2.562 | 1.667 - 3.938 | <0.0001 |
| **Age** | 1.004 | 0.984 - 1.025 | 0.6956 |
| **Race (Caucasian vs Non-Caucasian)** | 0.708 | 0.320 - 1.567 | 0.3948 |
| **BMI below 18.5** | 2.147 | 0.483 - 9.531 | 0.3152 |
| **BMI between 25 - 30** | 0.684 | 0.419 - 1.116 | 0.1281 |
| **BMI between 30 - 35** | 0.542 | 0.290 - 1.014 | 0.0553 |
| **BMI greater than 35** | 0.911 | 0.498 - 1.665 | 0.7613 |
| **Romano Comorbidity Score** | 1.019 | 0.951 - 1.092 | 0.5975 |

Given these findings, we did discuss with the basic science division at Washington University in St. Louis, regarding the potential underlying Biological rationale for this observed association of OS with a team of Chronobiologists. Given the long half-life of immune checkpoint inhibitors (weeks in most cases) and the typical treatment course being declared either successful or a failure after several cycles of treatment (typically 3-4) we decided to investigate the timing of the initial dose of immunotherapy as a predictor event.

**Figure 4: Lung cancer OS by Time of First Checkpoint Inhibitor Infusion: 10AM or earlier (red) vs after 1PM**

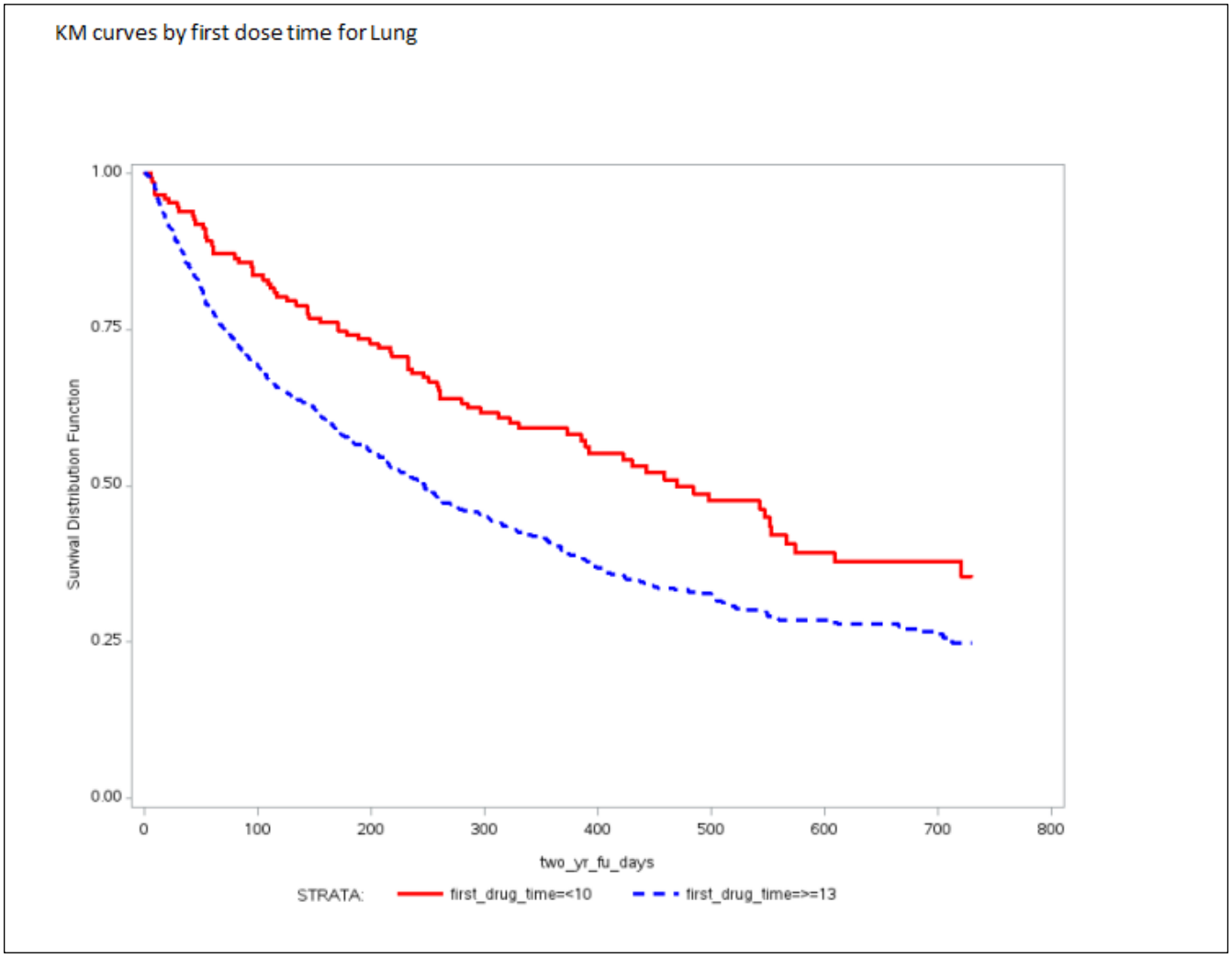
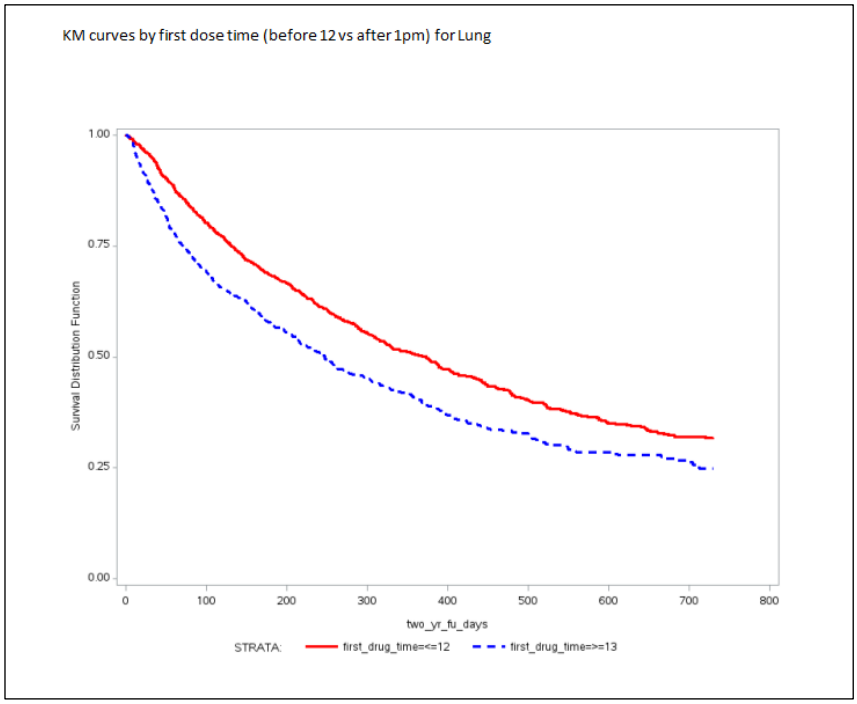


**Figure 5: Lung cancer OS by Time of First Checkpoint Inhibitor Infusion: 12PM or earlier (red) vs after 1PM**




We also investigated similar treatment times and outcomes in the Melanoma cohort. This is seen below in Figure 6 and Figure 7.

**Figure 6: Melanoma OS by Time of First Checkpoint Inhibitor Infusion: 12PM or earlier (red) vs after 1PM**

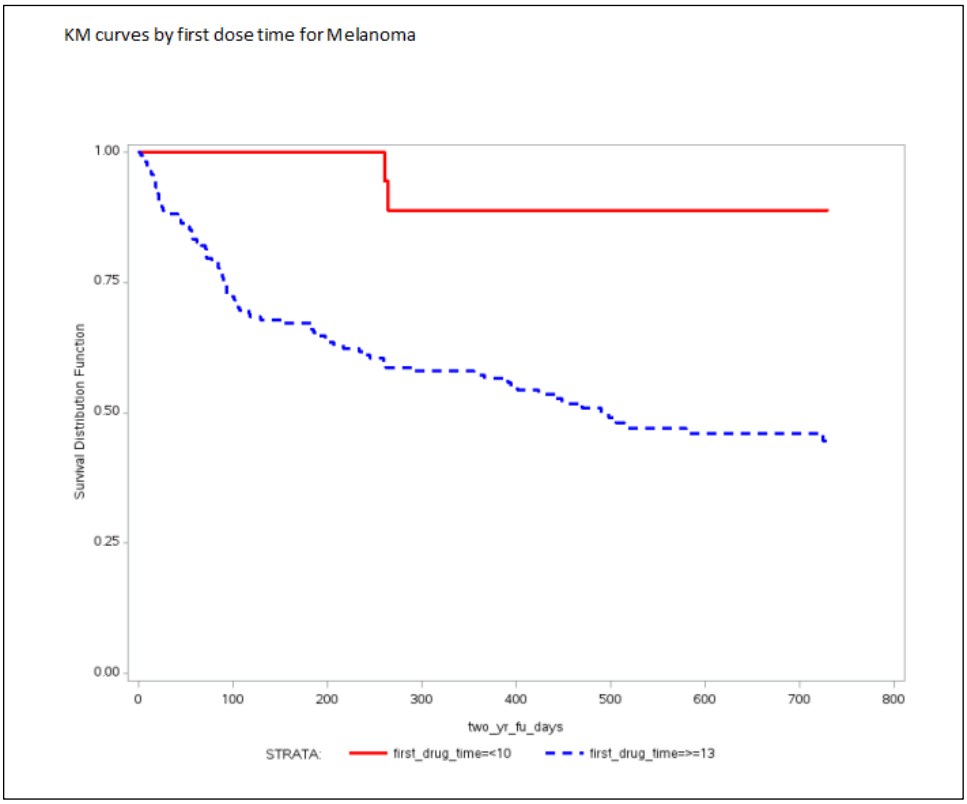
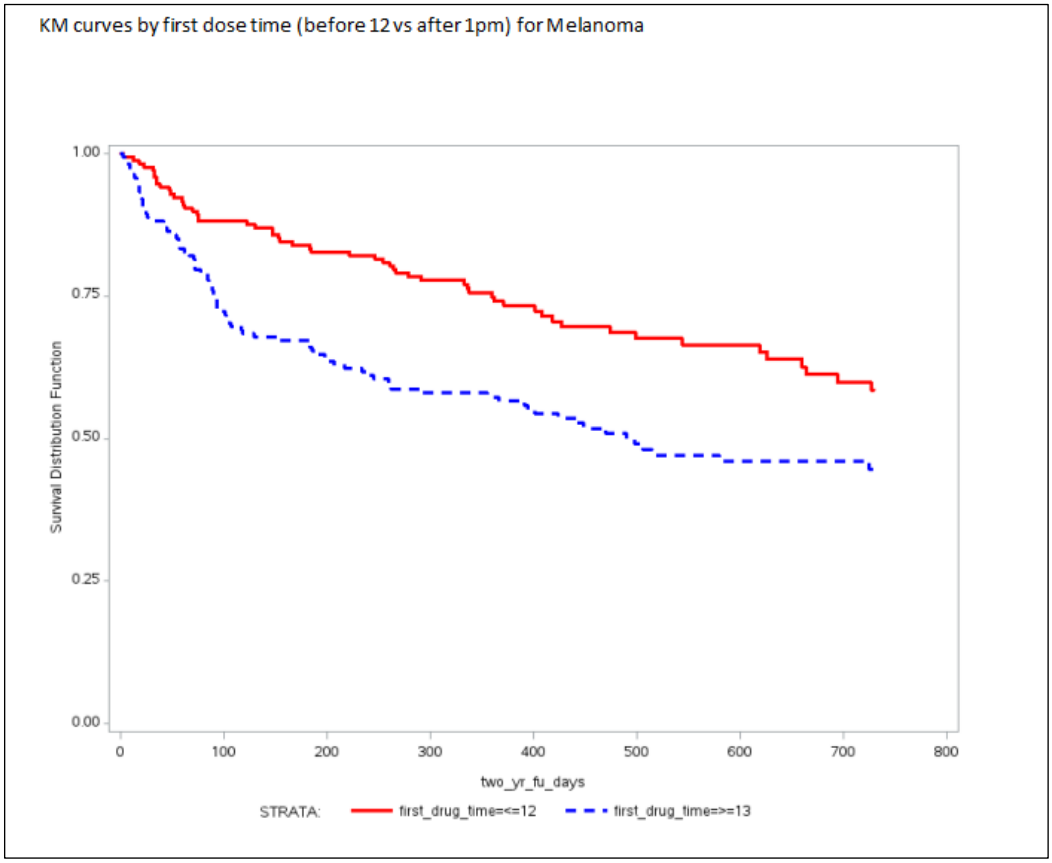


**Figure 7: Melanoma OS by Time of First Checkpoint Inhibitor Infusion: 12PM or earlier (red) vs after 1PM**




Expanding on these analyses we aimed to correct for the impact of frailty and potential difficulties with travel to and from the center by adjusting in multivariate models for distance from the treating center and utilizing a frailty score that was developed within the VA (Patel et al. *Frailty in Older Adults with Multiple Myeloma: A Study of US Veterans.* JCO Clin Cancer Inform. 2020 Feb;4:117-127). After inclusion of this scoring systems into the multivariate model and adding distance to the treating center, there was persistence of the survival advantage for early infusion time. A Propensity Score Matched model was created for Lung CA, Melanoma, Head & Neck SCC and Bladder cancer, controlling for age, comorbidities, distance to treating center and frailty, findings were positive in most disease states (all were negative in Renal Cell Cancer). Findings are presented below in Table 23.

**Table 23: Time of 1st ICI infusion and OS, Propensity Score Matched COX Model, Controlling for Age, Frailty, and Distance**

| Disease | Hazard Ratio for 1 Year OS | Hazard Ratio for 2 Year OS |
|---|---|---|
| Lung Cancer | 1.446 (1.028 - 2.032) | 1.656 (1.22 - 2.243) |
| Melanoma | 4.987 (1.593 - 15.608) | 2.960 (1.143 - 7.663) |
| Head and Neck SCC | 1.694 (0.947-2.948) | 2.525 (1.499 - 4.252) |
| Bladder Cancer | 2.582 (1.388 - 4.803) | 2.049 (1.230 - 3.414) |

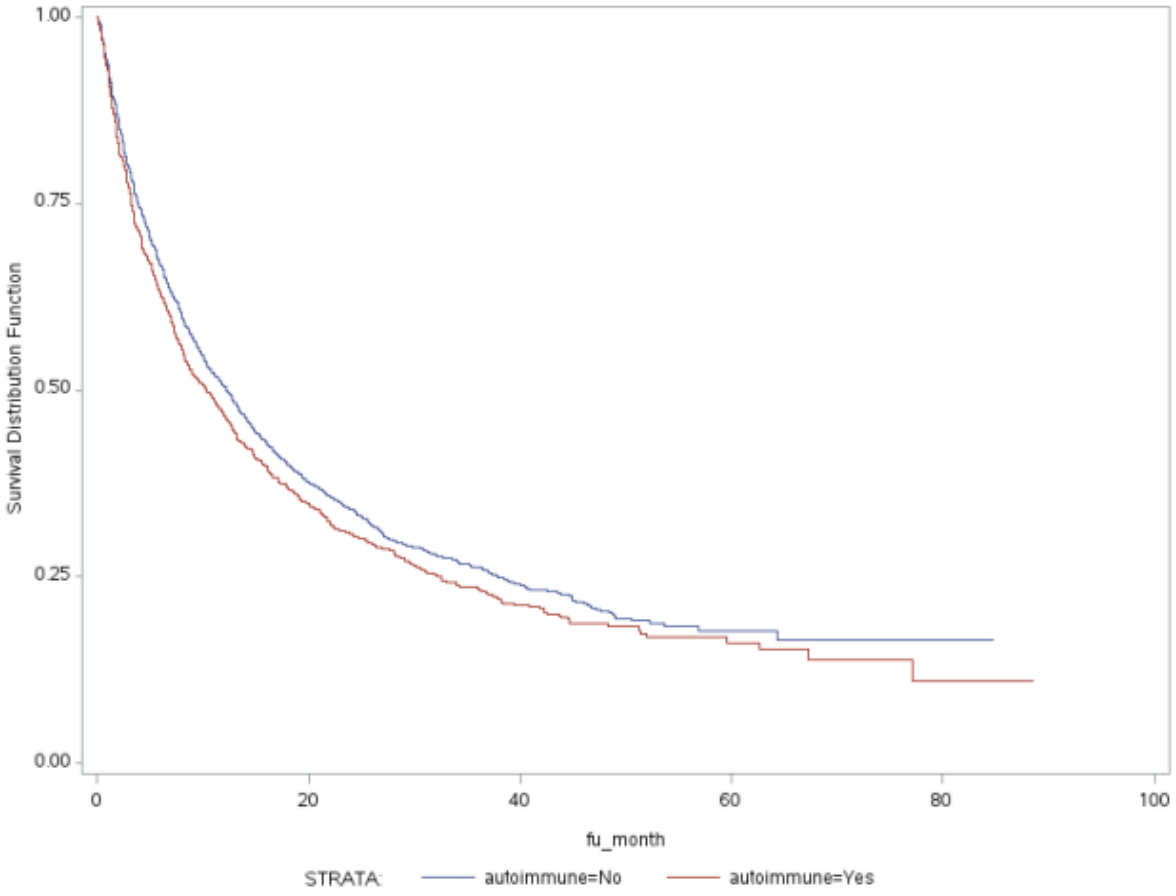
**At this time we are seeking publication of the findings as presented above regarding checkpoint inhibitor timing and improve Overall Survival. We have incorporated these findings into a proposal for a prospective clinical trial that is seeking funding through the Lung Precision Oncology Program through the Department of Veterans Affairs.**

Table 24: Autoimmune comorbidities among US Veterans receiving ICI for advanced cancer

| Diagnosis | number of pts |
|---|---|
| Rheumatoid Arthritis | 40 |
| Systemic Sclerosis | 1 |
| Systemic Lupus Erythematosus | 8 |
| Sjogren Syndrome | 10 |
| Polymyositis | 0 |
| Systemic Connective Tissue Disorders | 28 |
| Wegeners Granulomatosis | 0 |
| Dermatomyositis | 0 |
| Raynaud's Syndrome | 127 |
| Sarcoidosis | 9 |
| Autoimmune Hemolytic Anemia | 3 |
| Immune Thrombocytopenic Purpura | 1 |
| Guillain-Barre Syndrome | 24 |
| Myasthenia Gravis | 1 |
| Giant Cell Arteritis | 124 |
| Autoimmune Disease, NOS | 0 |
| Hashimotos Thyroiditis | 0 |
| Grave's Disease | 9 |
| Ankylosing Spondylitis | 134 |
| Celiac Disease | 4 |
| Inflammatory Bowel Disease | 135 |
| Psoriasis and Psoriatic Arthritis | 69 |
| Autoimmune Hepatitis | 3 |
| Primary Biliary Cirrhosis | 2 |
| Polyarteritis Nodose | 1 |
| Pemphigus Vulgaris | 0 |
| Vasculitis, Limited to Skin, Unspecified | 4 |
| Thyroiditis | 8 |
| Hyperthyroidism, NOS | 337 |
| Gout | 233 |
| Crystal Arthropathies | 5 |
| Spondyloarthropathies | 0 |
| Interstitial Cystitis | 2 |
| Primary Sclerosing Cholangitis | 0 |
| Vitiligo | 12 |
| Undifferentiated Connective Tissue Disorder | 2 |

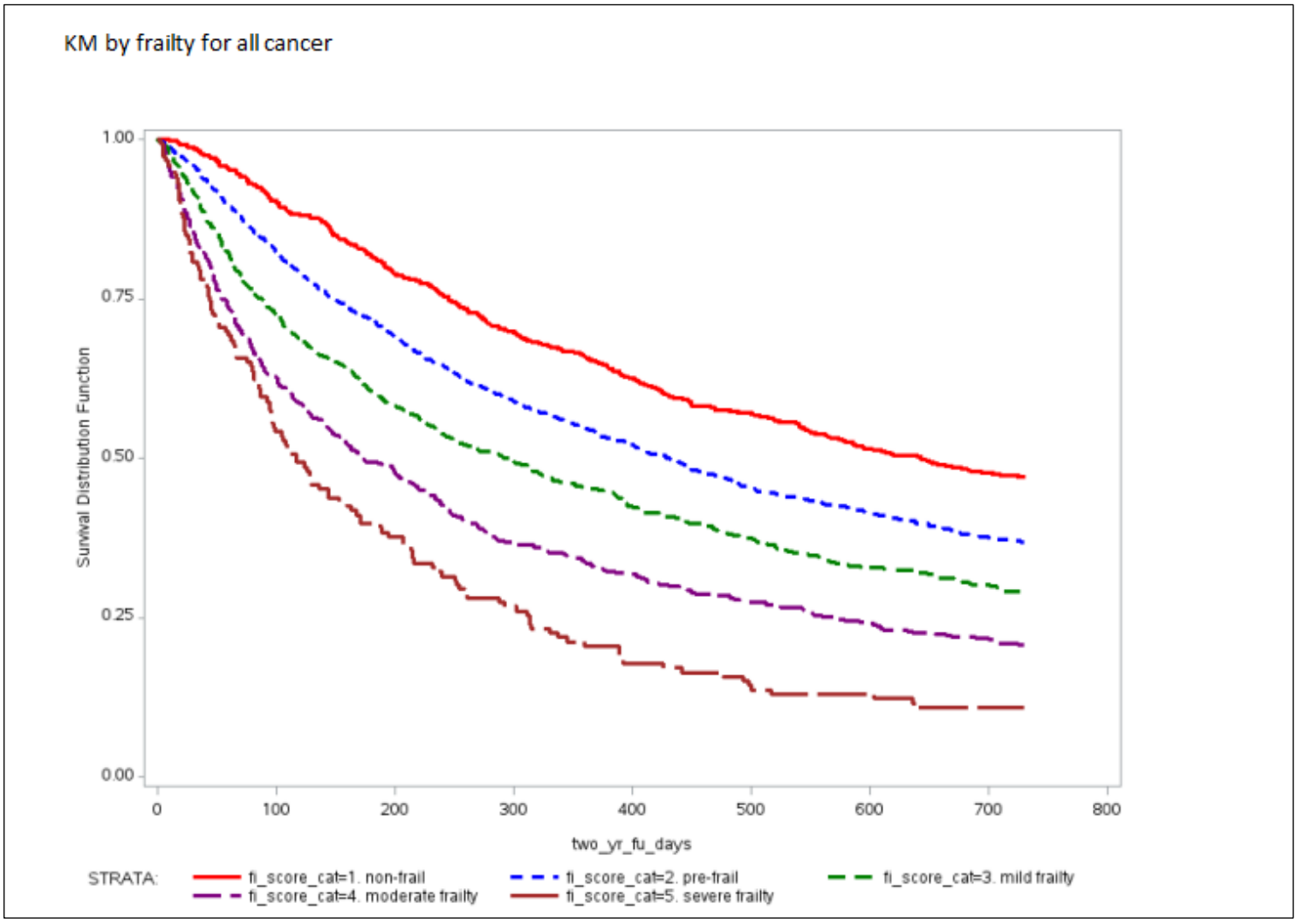
**Presented in Table 24 is an additional predictor of OS among patients undergoing immunotherapy for advanced cancer is the existence of a prior autoimmune comorbidity. The impact of autoimmune toxicities among this population is likewise under evaluation. Utilizing a list of ICD-9 and ICD-10 codes for prior autoimmune toxicities we have identified a set of patients with pre-existing autoimmune conditions and have analyzed survival of patients with pre-existing autoimmune comorbidity versus their counterparts without autoimmune comorbidities. Survival on immunotherapy appears worsened among US Veterans receiving ICI with a prior autoimmune comorbidity. The potential of this as a predictor for OS and autoimmune toxicities is being evaluated in additional studies. Kaplan-Meier assessment of survival among patients with autoimmune comorbidities versus their healthy counterparts is presented in Figure 8.**

Figure 8: Overall Survival Among Patients with Pre-existing Autoimmune Comorbidities




**As an additional predictor of outcomes among VA patients undergoing treatment with ICI for advanced cancers, we applied the frailty scoring system utilized in prior analyses of time of treatment to see if it was an effective measure of outcomes among ICI recipients. This frailty score was developed among a US Veteran population (Patel et al. *Frailty in Older Adults with Multiple Myeloma: A Study of US Veterans.* JCO Clin Cancer Inform. 2020 Feb;4:117-127). Categorizing patients by frailty scoring showed a clear distinction of OS among frailty classes (see Figure 9).**

Figure 9: Overall Survival among ICI recipients by Frailty Category, Whole Cohort




**Above, frailty categories and OS are calculated for non-frail, pre-frail, mild frailty, moderate frailty and severe frailty with clear distinction of outcomes for ICI recipients (See Figure 9). Given these initial findings, additional evaluations were performed with assessment of OS among ICI recipients across disease states and subsequent analyses evaluating consolidated frailty categories. Seen in Figure 10 for Lung cancer patients, and Figure 11 for Head and Neck SCC. To better assess patients, we consolidated frailty categories from 5 down to 3 (non-frail, pre/mild frailty, mod/severe frailty). Patient characteristics of these consolidated frailty classes were compared in Table 25, findings support clear divisions among these classes. To further assess findings of OS among these classes, we performed Kaplan-Meier assessment of OS among frailty categories in the entire cohort (Figure 12), and among the Lung cohort (Figure 13) and Melanoma cohort (Figure 14). Overall findings were shown to be effective at dividing patients into different OS categories. To further assess we performed OS analysis of patients within our Washington University in St. Louis cohort displayed in Figure 15 and 16, below.**

Figure 10: Overall Survival among ICI recipients by Frailty Category, Lung Cancer Cohort

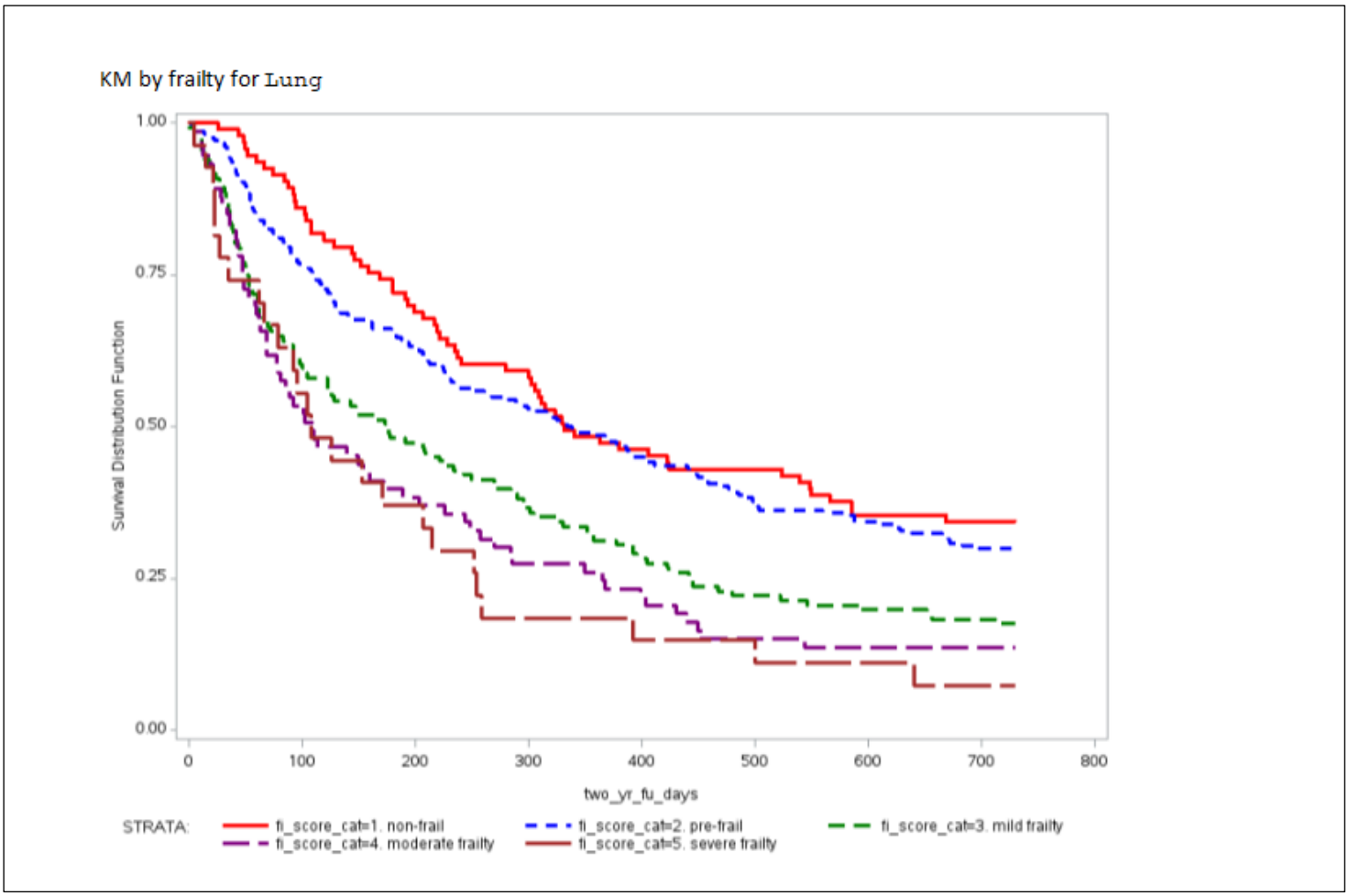



Figure 11: Overall Survival among ICI recipients by Frailty Category, Head and Neck Cancer Cohort

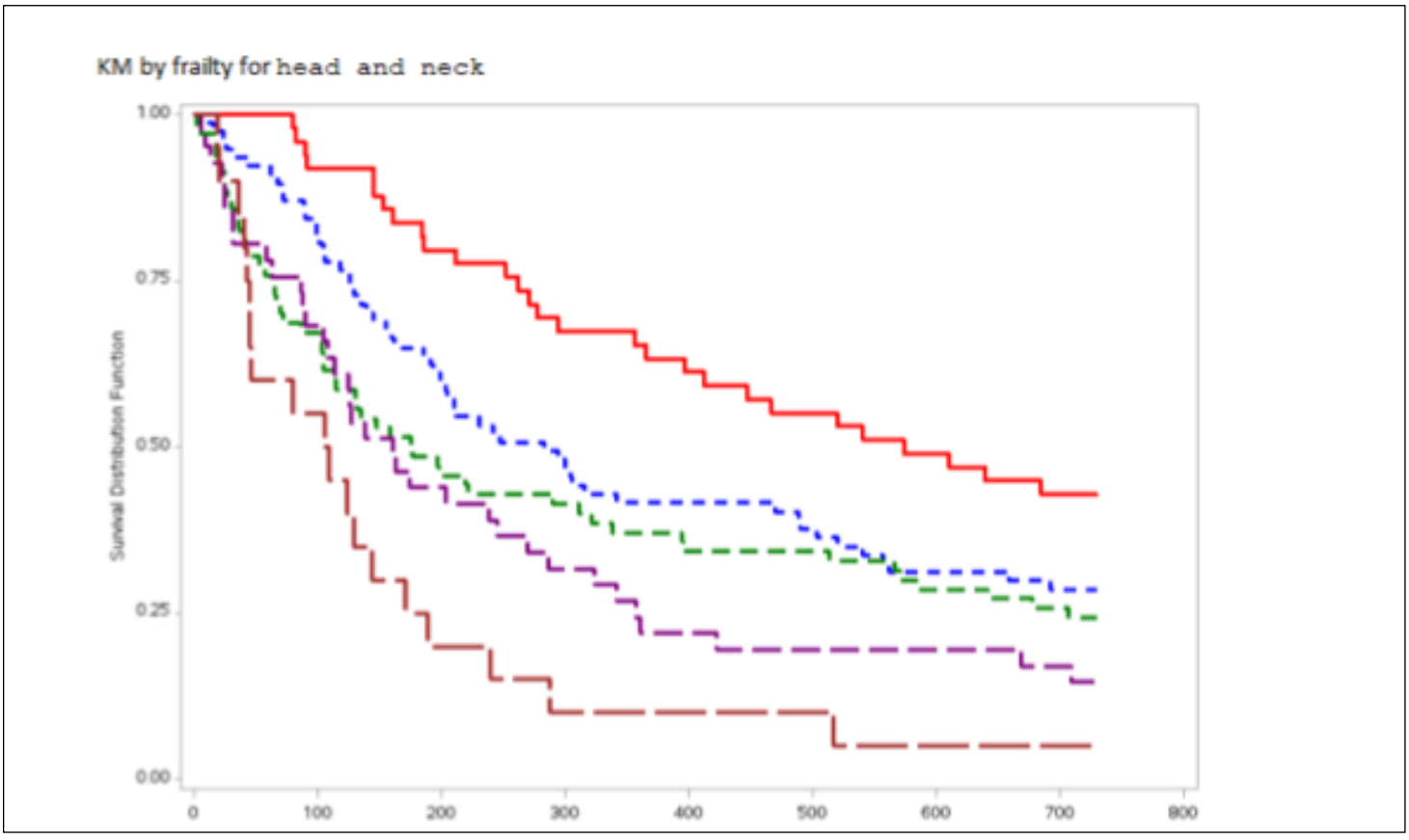


TABLE 25: Characteristics of Frailty cohorts, division into three frailty categories

| Demographic clinical characteristics | Entire cohort (N=3169) non-frailty n=135 | pre or mild frailty n=1618 | moderate or severe frailty n=1416 | P-value |
|---|---|---|---|---|
| Age (mean years) | 64.6 | 67.9 | 69.4 | <0.001 |
| Male (%) | 97 | 96.5 | 97 | 0.73 |
| Charlson score index (mean) | 0.96 | 3.3 | 5.9 | <0.001 |
| Race (%) | | | | 0.052 |
| White | 86.7 | 82.6 | 79.9 | |
| non-white | 13.3 | 17.4 | 20.1 | |
| BMI categroy (%) | | | | 0.06 |
| Bmi<30 | 85.2 | 78.2 | 76.6 | |
| BMI>=30 | 14.8 | 21.8 | 23.4 | |

| Demographic clinical characteristics | Lung with Nivo cohort (N=3169) non-frailty n=16 | pre or mild frailty n=233 | moderate or severe frailty n=271 | P-value |
|---|---|---|---|---|
| Age (mean years) | 65.1 | 69 | 68.7 | 0.14 |
| Male (%) | 100 | 97.9 | 95.6 | 0.27 |
| Charlson score index (mean) | 1.3 | 3.7 | 5.3 | <0.001 |
| Race (%) | | | | 0.63 |
| White | 75.0 | 77.7 | 80.8 | |
| non-white | 25.0 | 22.3 | 19.2 | |
| BMI categroy (%) | | | | 0.15 |
| Bmi<30 | 93.8 | 82 | 77.1 | |
| BMI>=30 | 6.3 | 18 | 22.9 | |

Figure 12: Overall Survival among ICI recipients by Consolidated Frailty Category, Entire Cohort

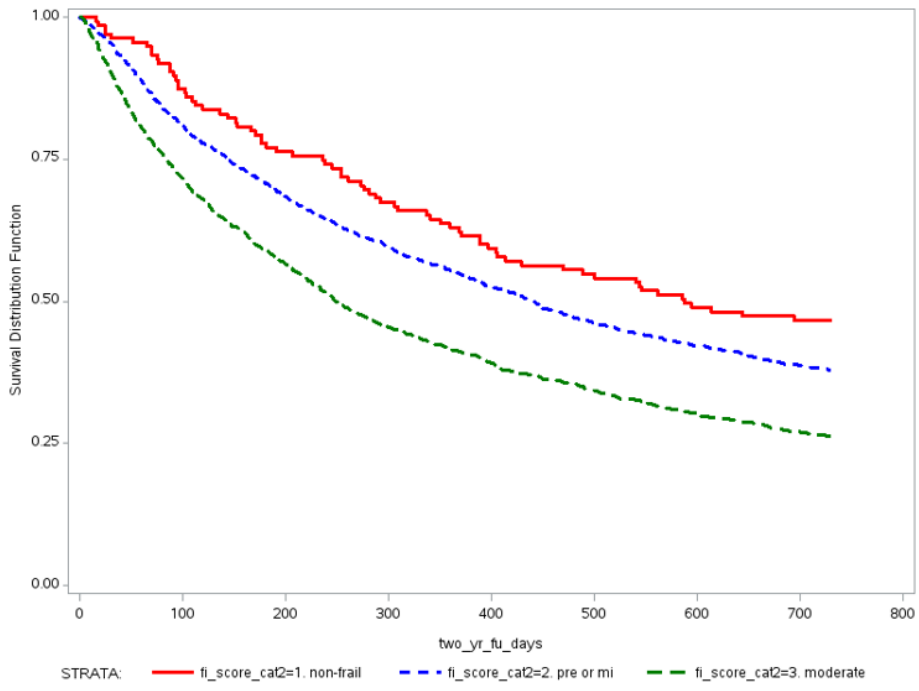


Figure 13: Overall Survival among ICI recipients by Consolidated Frailty Category, Lung Cohort

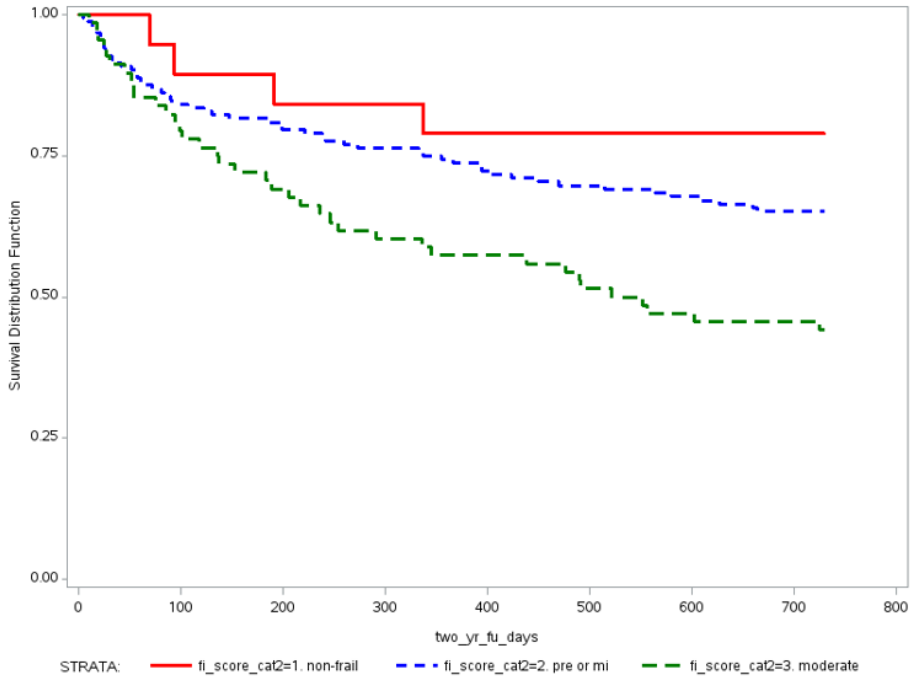



Figure 14: Overall Survival among ICI recipients by Consolidated Frailty Category, Melanoma Cohort

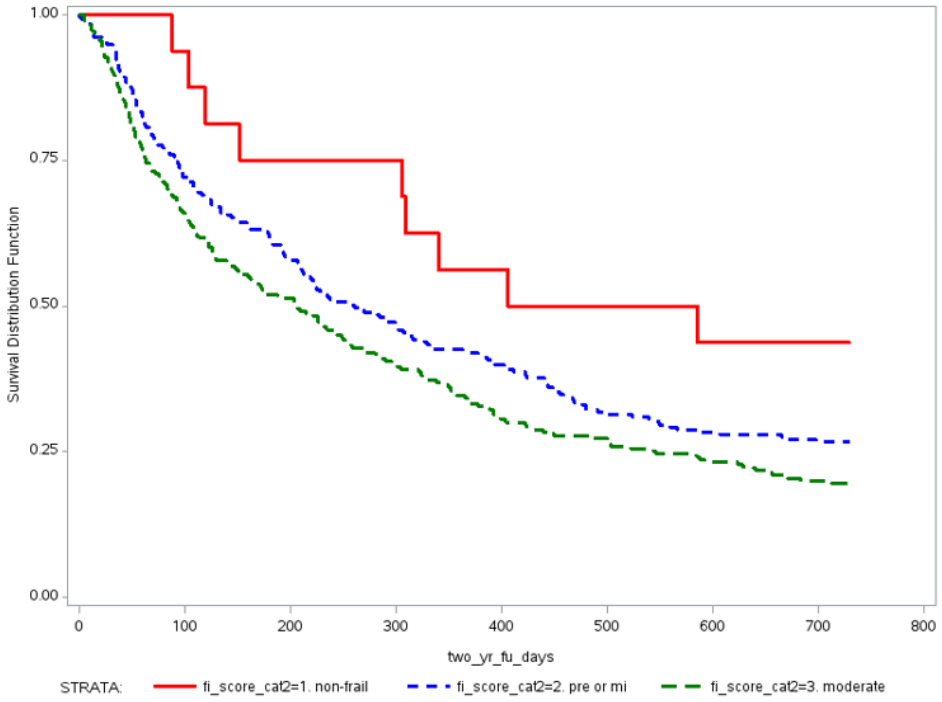
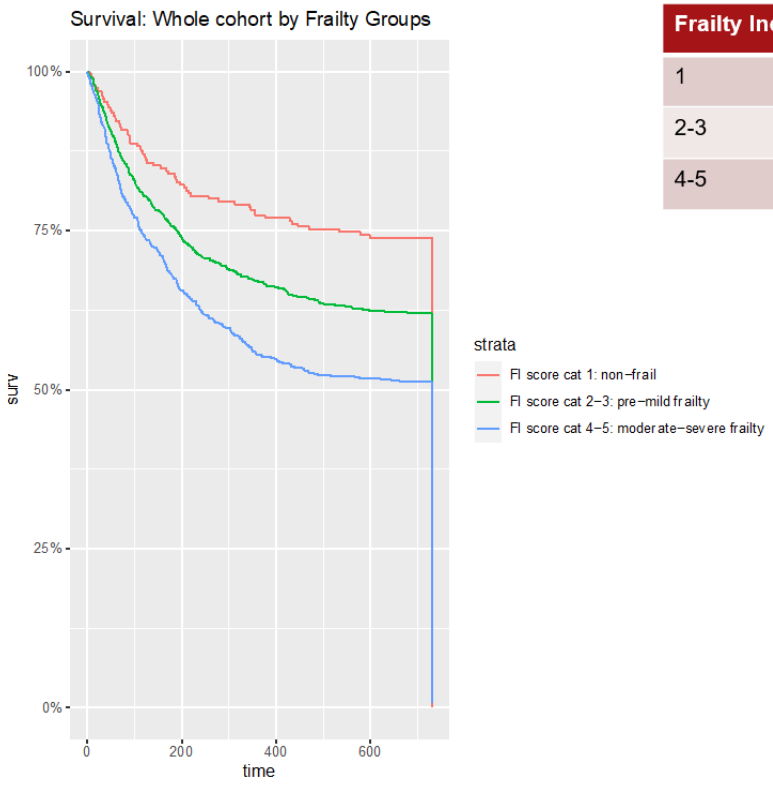
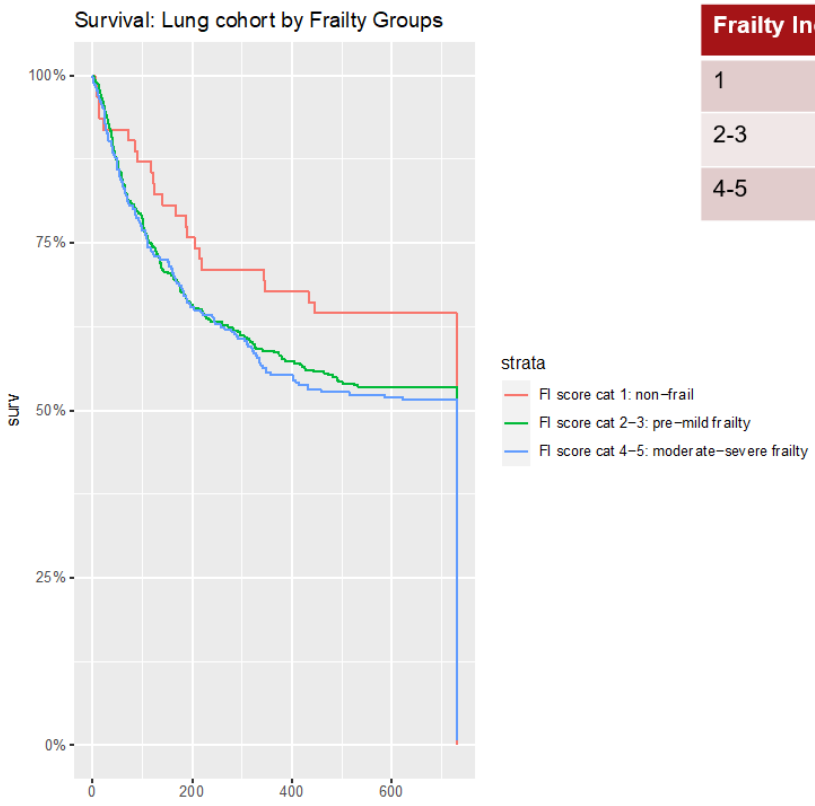


Figure 15: Overall Survival among ICI recipients by Consolidated Frailty Category, Entire Cohort (WUSTL Data)




| Frailty Index Category | Number of patients |
|---|---|
| 1 | 230 |
| 2-3 | 902 |
| 4-5 | 623 |

Figure 16: Overall Survival among ICI recipients by Consolidated Frailty Category, Lung Cohort (WUSTL Data)




| Frailty Index Category | Number of patients |
|---|---|
| 1 | 62 |
| 2-3 | 389 |
| 4-5 | 277 |

- ***Subtask 4: Exclusion of covariate pairs with strong correlation in VA dataset***
    - Initial analyses have not revealed significant correlation among covariate pairs within candidate predictors.
- ***Subtask 5: Multivariate analysis and finalization of the model in VA dataset***

Table 26 presents a multivariate model for risk factors associated with Prednisone prescription from the VA dataset. These will serve as predictors in the final model. Additional work is proceeding on this portion of the study, limited by pace of abstraction to date.

**Table 26: Multivariate association with Prednisone Prescription (Autoimmune Toxicity) in VA cohort**

| Effect | Odds Ratio Estimate | 95% Confidence Interval |
|---|---|---|
| BMI (BMI < 18.5 vs BMI 18.5 - 25) | 0.633 | 0.394 - 1.019 |
| BMI (BMI 25 - 30 vs 18.5 - 25) | 1.092 | 0.848-1.406 |
| BMI (BMI 30 - 35 vs 18.5 - 25) | 1.557 | 1.141-2.123 |
| BMI (BMI > 35 vs BMI 18.5 - 25) | 1.291 | 0.853-1.955 |
| Hemoglobin (10-13 vs >13) | 0.872 | 0.692-1.101 |
| Hemoglobin (<10 vs >13) | 0.506 | 0.355 - 0.722 |
| Albumin (3-3.5 vs >3.5) | 0.941 | 0.737 - 1.202 |
| Albumin (< 3 vs > 3.5) | 0.681 | 0.497 - 0.932 |
| Diabetes Mellitus | 0.736 | 0.588 - 0.920 |
| Renal Disease | 1.607 | 1.056 - 2.446 |
| Lung Disease | 1.315 | 1.034 - 1.673 |
| Nivolumab Use | 0.729 | 0.529 - 1.003 |
| Pembrolizumab Use | 0.659 | 0.477 - 0.910 |
| Atezolizumab Use | 0.506 | 0.295-0.865 |

- ***Subtask 6: Validation of the model utilizing WUSTL dataset***
    - **Work on this Subtask is ongoing currently. Work at WUSTL is somewhat limited given movement of the grant to a no cost extension status.**

## MAJOR TASK 4: *To develop a machine learning based risk prediction model*

*Task Overview:* The bulk of this task is still sometime in the future, and work continues on the process of setting up the model, denoting and cleaning the data, as well as appropriately identifying autoimmune toxicity events so that the model is accurate and effective. We have developed the basic framework for the model at this time and have run a preliminary attempt at model derivation. Initially, we had planned to use the *Autoprognosis* python model to develop the machine learning model, but we have abandoned this approach to utilize more traditional protocols in model development. This is mainly due to increased machine learning expertise among our research staff (Dr. Inez Oh).

- *Subtask 1: Cleaning/Denoting dataset for ML protocols*
    - We have completed cleaning and denoting of the dataset for ML protocols and have results from ML analyses on the Washington University in St. Louis cohort.

- *Subtask 2: Utilization of Autoprognosis python module to develop ML mode*
    - We have moved on from Autoprognosis and are using pure Python based approaches to implement ML analyses.
- *Subtask 3: Utilization of manual ML protocols to develop routine ML model*
    - Given improvement in ML capabilities we are using Python based approaches to develop ML models and proceed with ML analyses.

Initial ML models for predictors of irAEs and Overall Survival at 1 and 2 years are presented below. In Table 27 and 28, candidate models and predictors are presented. In Figure 17, a Machine Learning Random Forest model is presented showing predictors of autoimmune toxicity. These are presented in Shapley Additive Explanation (SHAP) plots. Figure 9 displays a K-nearest neighbor (KNN) model of autoimmune toxicity development. In these plots, more important features (variables) are higher in the list. Figures 19-20 present a model for risk of death at 1 year via a logistic regression and xtree model. Figure 21-22 presents a model for risk of death at 1 year via a logistic regression and xtree model. These are ML models for prediction of overall survival and immune toxicity development.

**Table 27: Machine Learning Model Approaches Utilized**

| ML Models Utilized |
|---|
| Parameter Grid-Search |
| 5-fold cross-validation |
| Logistic Regression |
| Decision Tree |
| Random Forest |
| Extra Trees |
| Gradient Boosting Classifier |
| K-nearest Neighbors |

**Table 28: Sample Features assessed in ML Models**

| Features Utilized in Model |
|---|
| Sex |
| BMI |
| Race |
| Cancer Diagnosis |
| Checkpoint Inhibitor |
| Creatinine |
| Hemoglobin |
| Albumin |
| MI |
| Hepatitis |
| HF |
| PVD |
| Renal Disease |
| HIV |
| Liver Disease |
| Diabetes |
| COPD |

Figure 17: ML Model Feature Components (SHAP Plot) iRAE Development, Random Forest Model

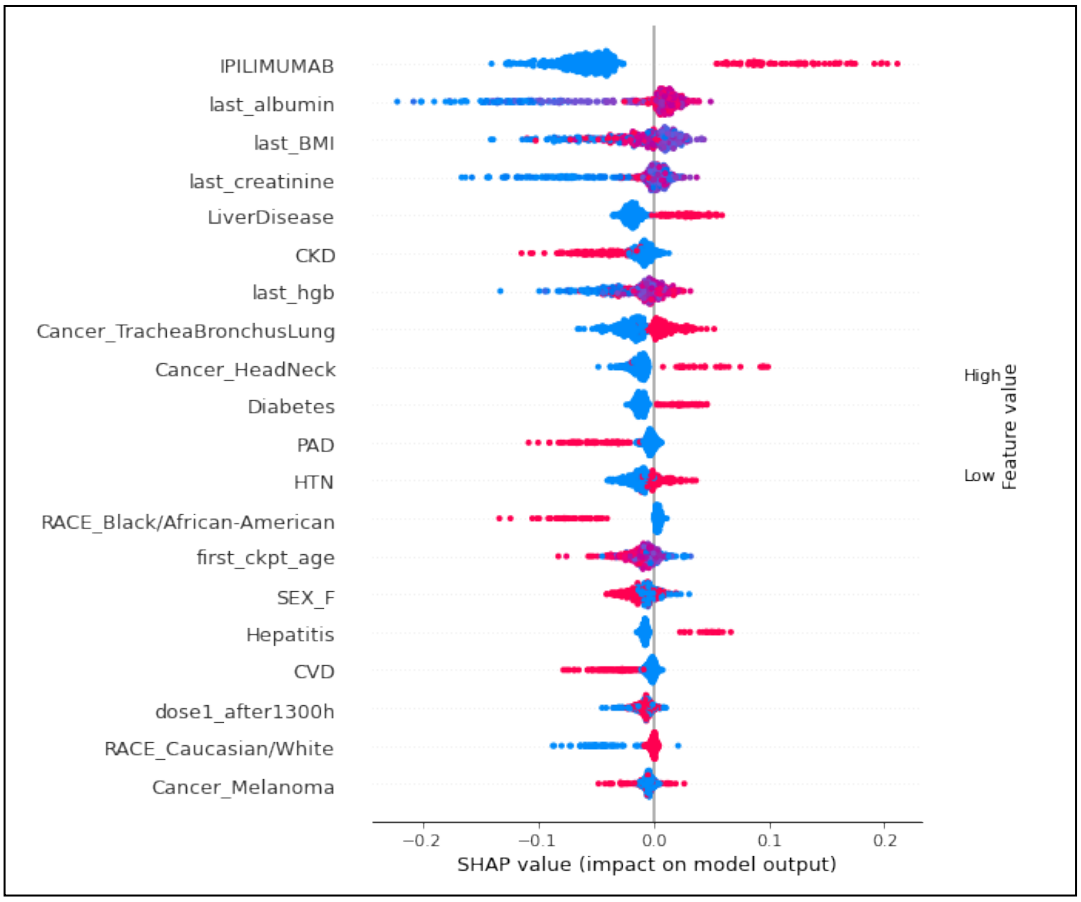



Figure 18: ML Model Feature Components (SHAP Plot) iRAE Development, KNN Model

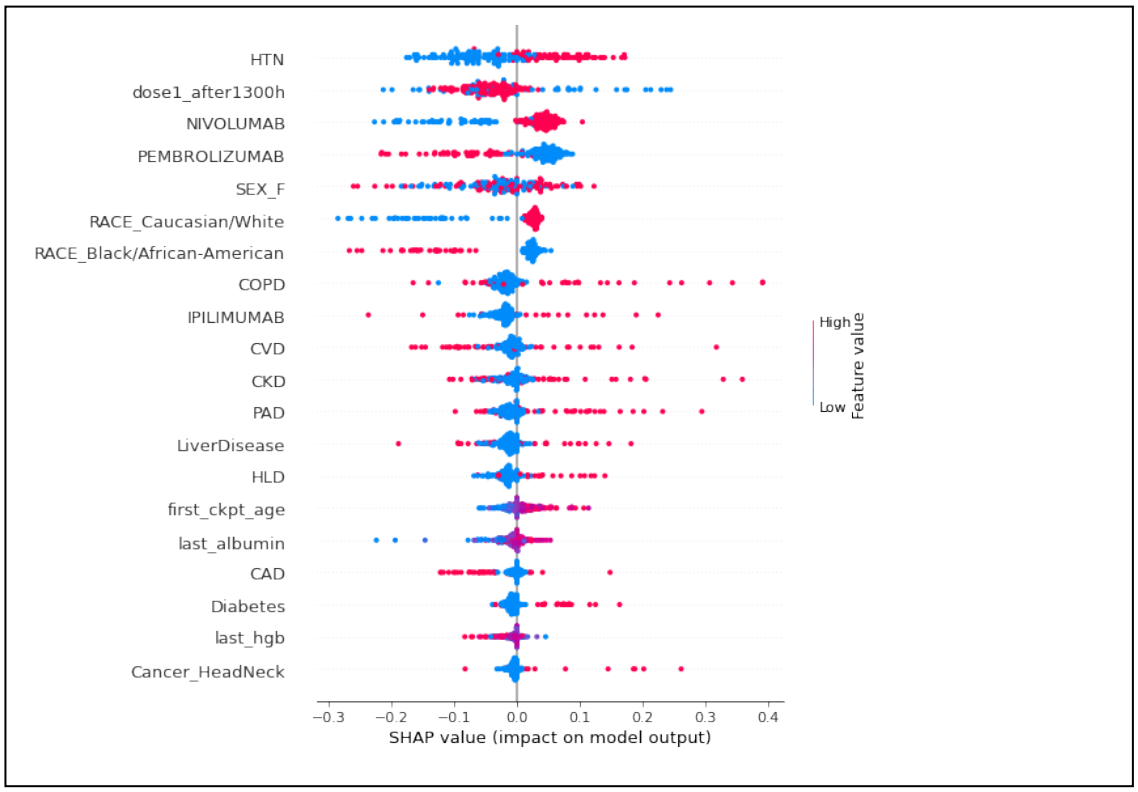


Figure 19: ML Model Feature Components (SHAP Plot) Death at 1 Year, Logistic Regression Model

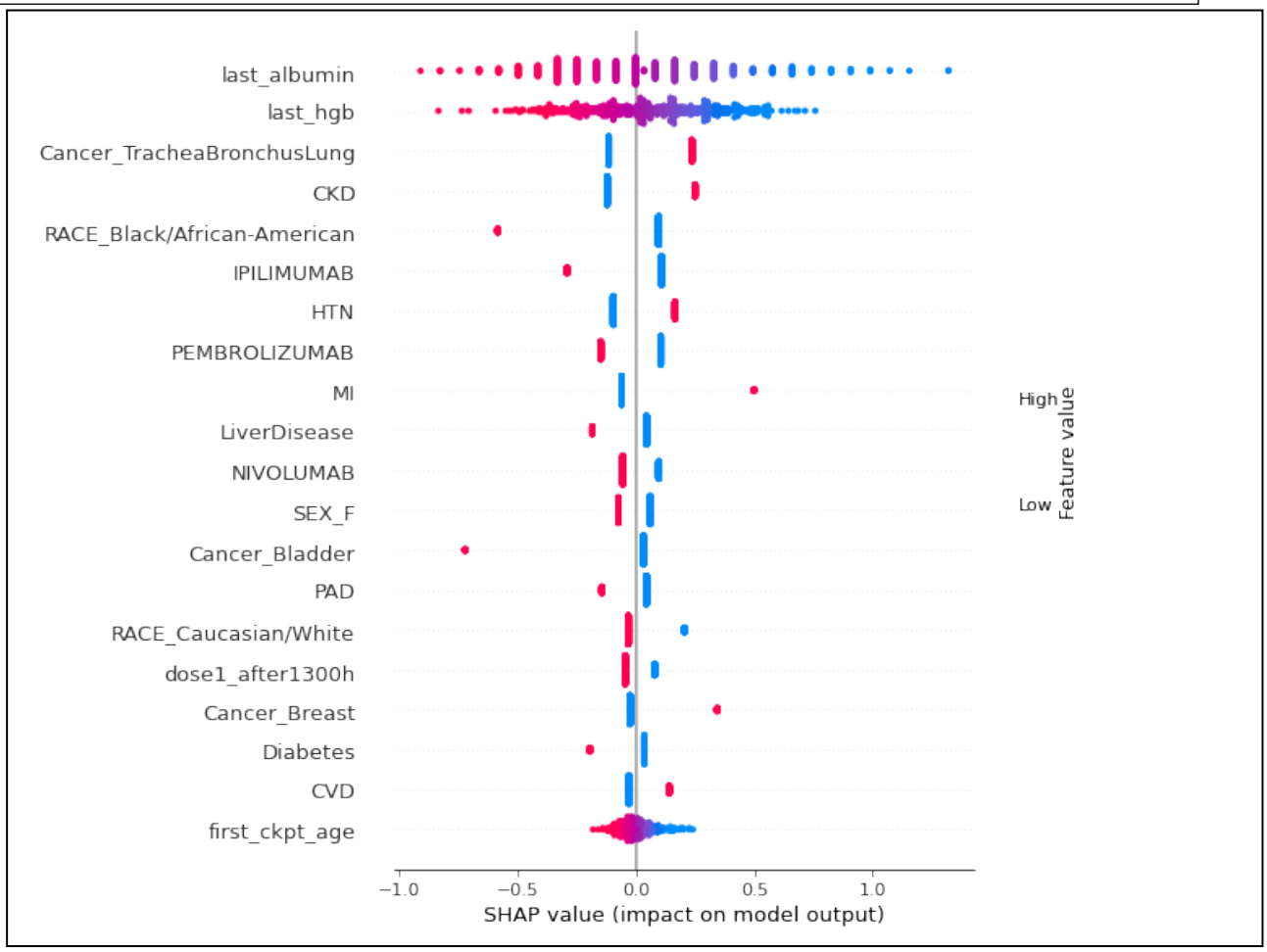



Figure 20: ML Model Feature Components (SHAP Plot) Death at 1 Year, XTREE Model

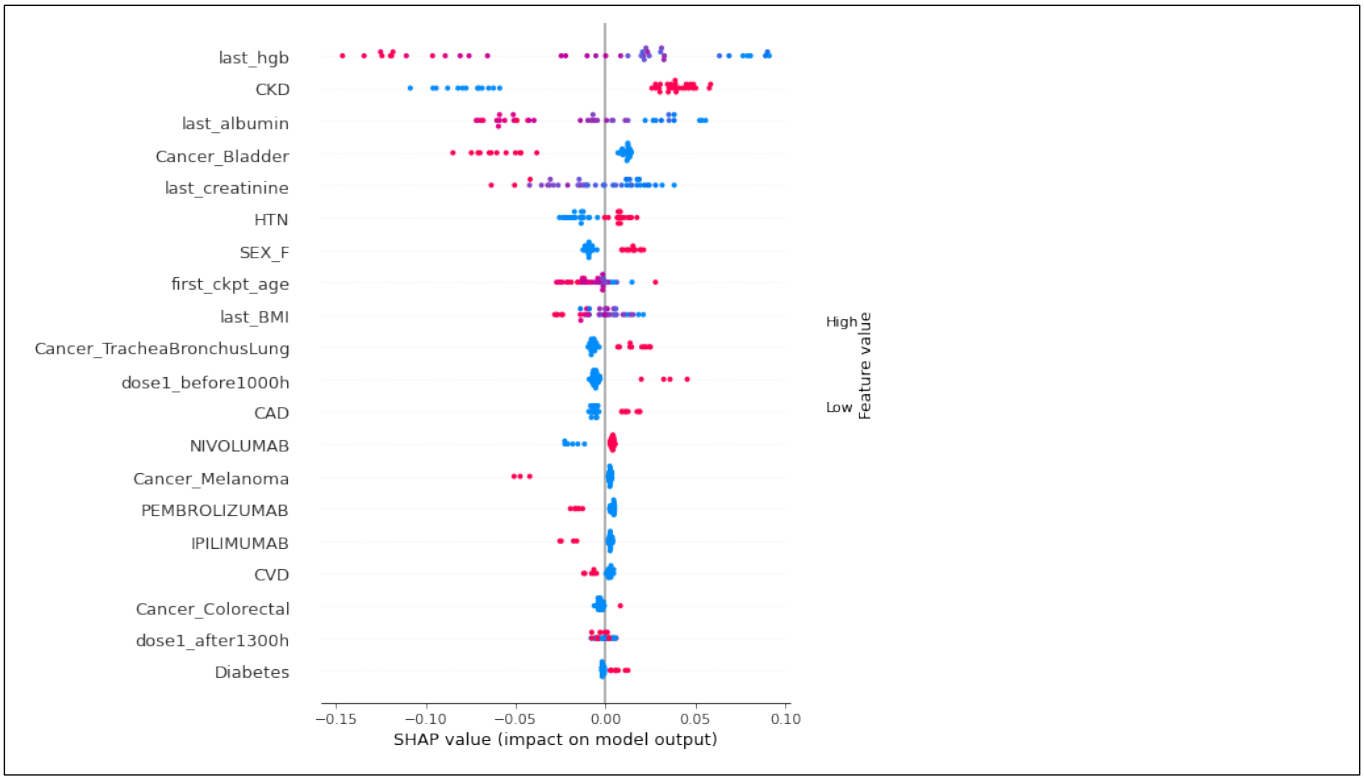


Figure 21: ML Model Feature Components (SHAP Plot) Death at 2 Years, Logistic Regression Model

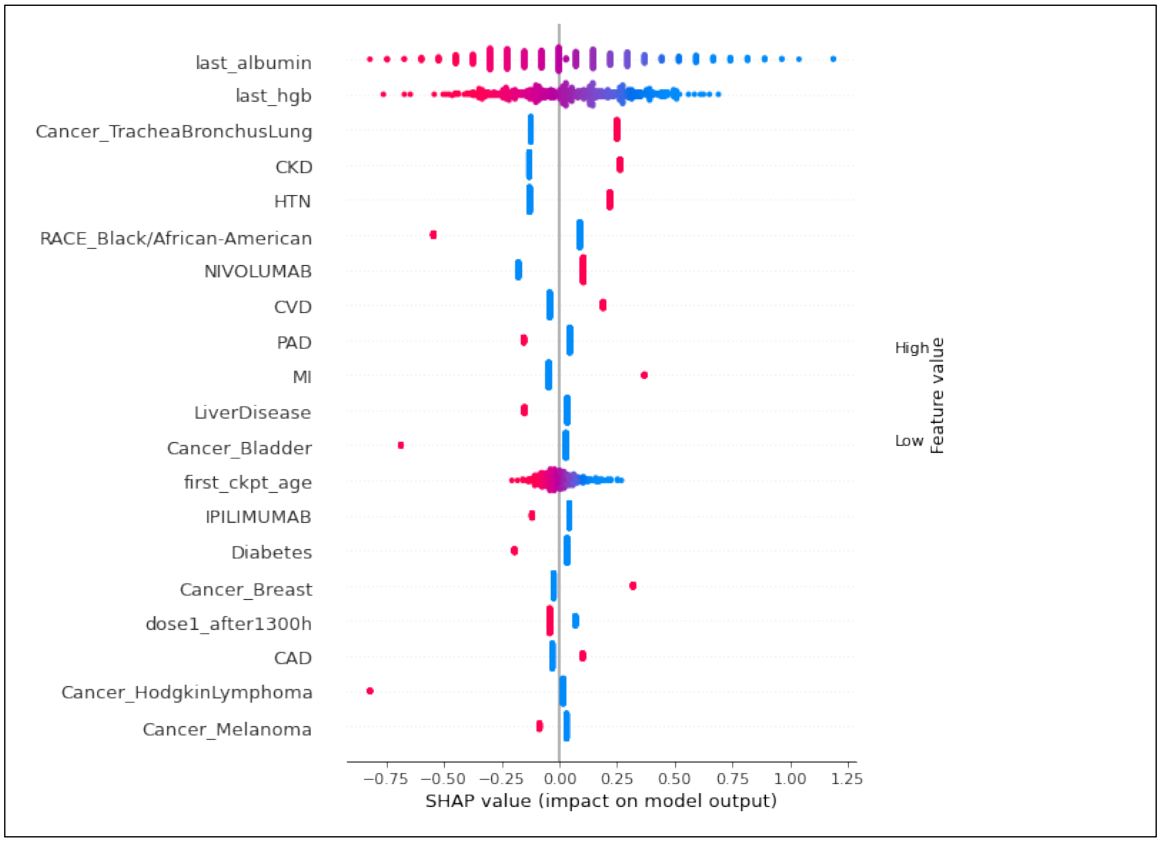
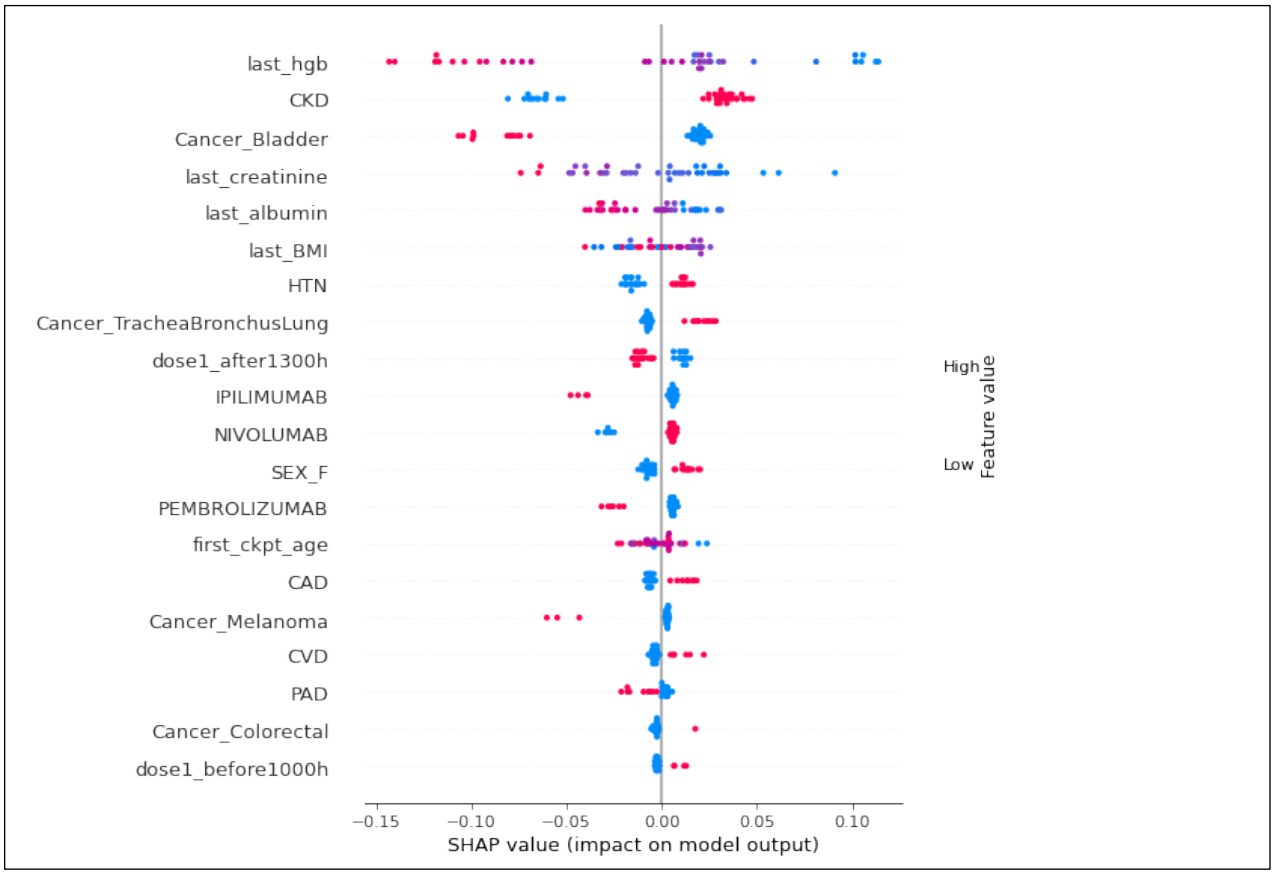



Figure 22: ML Model Feature Components (SHAP Plot) Death at 2 Years, XTREE Model



- *Subtask 4: Comparison of ML models (Autoprognosis vs Routine)*
    - This task is no longer necessary given our approach of utilizing pure Python routines as opposed to Autoprognosis.
- *Subtask 5: Validation of optimal ML model with WUSTL data*
    - We have made substantial progress on this approach.
- *Subtask 6: Comparison of optimal ML model with Regression based model*
    - This task is ongoing and pending completion of other associated and dependent tasks.
- *Subtask 7: Preparation of manuscript and publication of results*
    - **Some manuscripts have been submitted and published as detailed in Appendix.**

**MAJOR TASK 5:** *To correlate development of autoimmune toxicities with PFS and OS as compared to those not developing toxicity*

- *Subtask 1: Calculate OS utilizing disease specific survival data*
    - We have completed OS calculations for cohorts at the VA and WUSTL. These data are included and necessary for the models and calculations as above and will not be presented on their own.
- *Subtask 2: Calculate OS and PFS data for patients with grade 3/4 toxicities*
    - We have calculated OS data for patients with grade 3/4 toxicities from ICI therapy as identified by various mechanisms, including ICD codes and Prednisone prescriptions.

Figure 23: Overall Survival for all cancer diagnoses from VA data among Prednisone recipients (autoimmune toxicity) vs No Prednisone

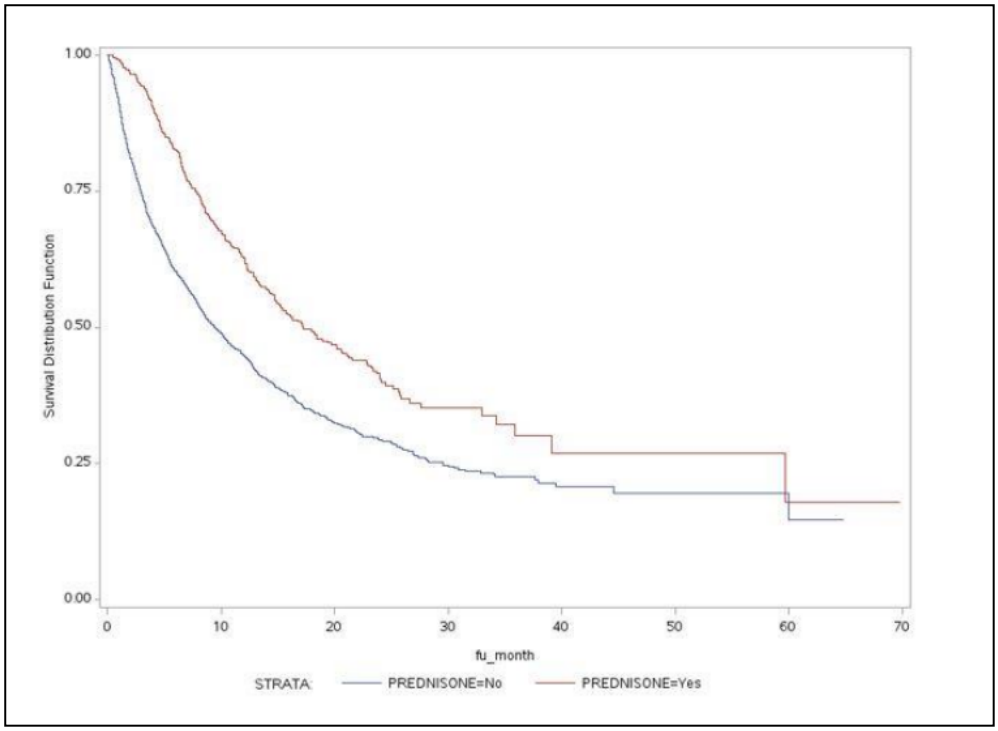
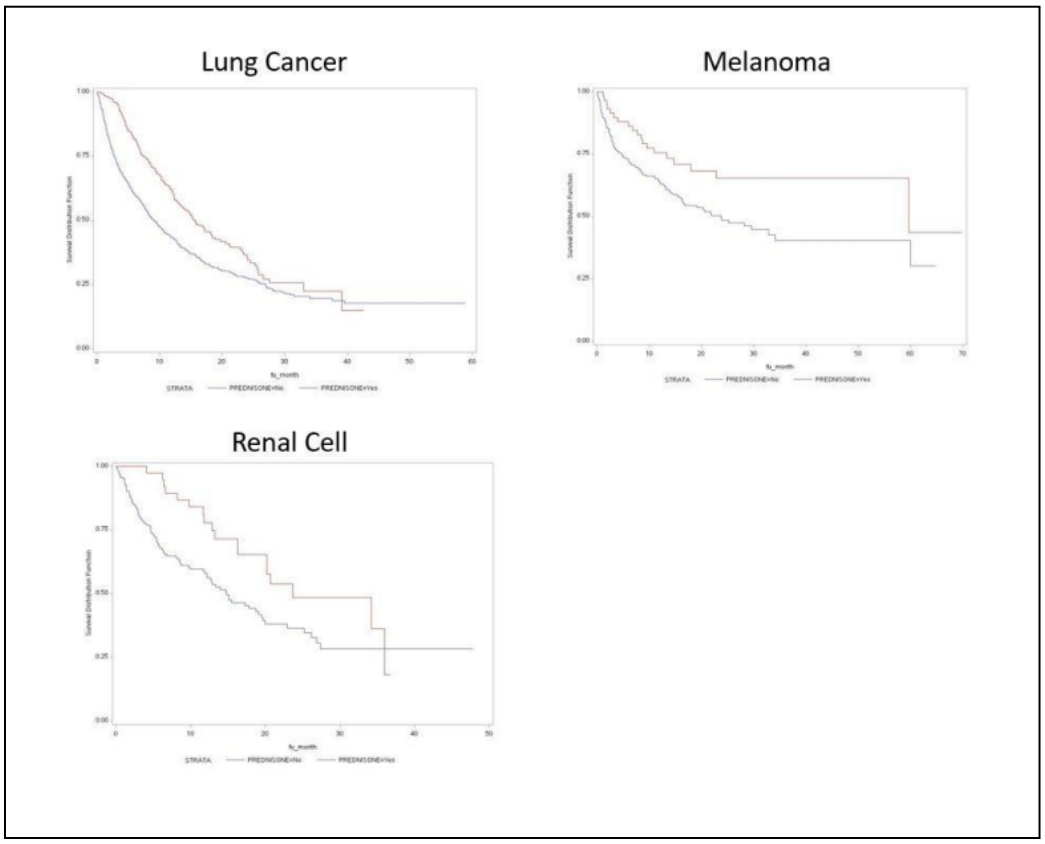


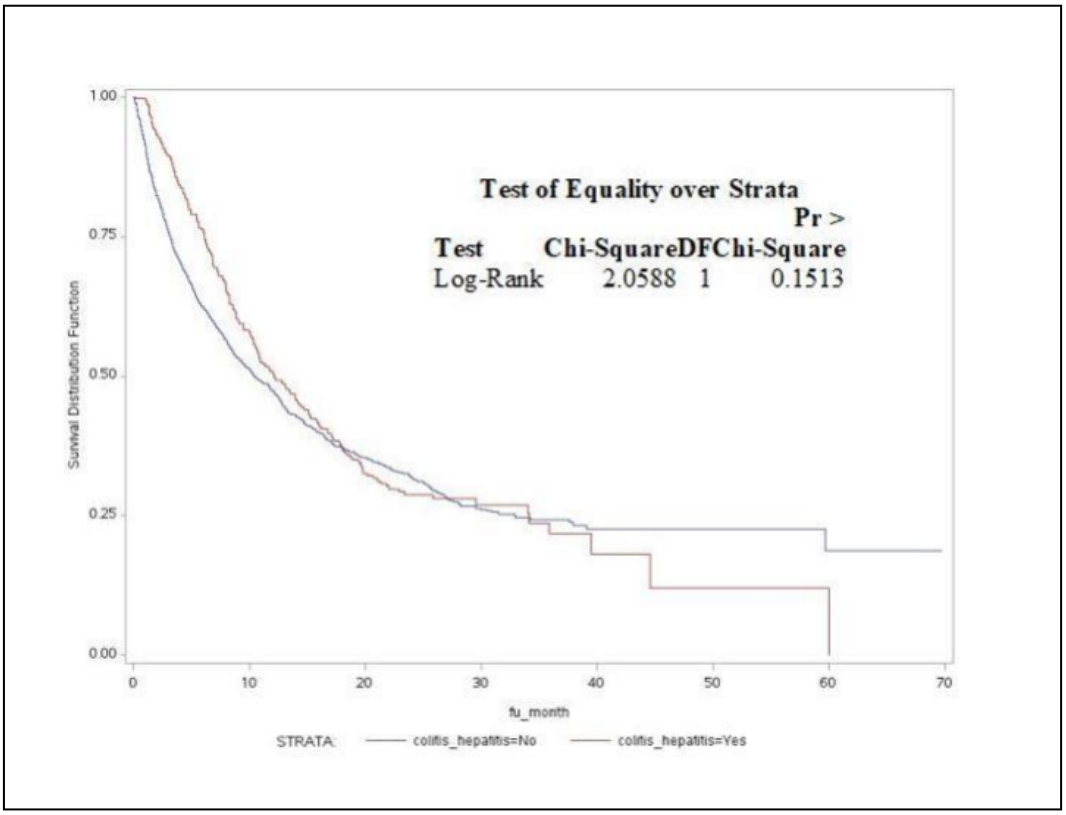
Figure 23 above shows a Kaplan-Meier survival analysis for patients from all cancer diagnoses who received ICI therapy, comparing those patients who received a prescription of prednisone during or within 6 months of completion of ICI treatments versus those who did not. Improved OS was observed and was statistically significant for patients receiving a prednisone prescription between the initial dose of ICI therapy and 6 months post ICI therapy concluded.

Figure 24: Overall Survival for Lung, Melanoma and Renal Cell among VA patients receiving Prednisone vs Not




Above in Figure 24, the findings outlined in Figure 2 are examined for key cancer diagnoses of melanoma, lung cancer and renal cell carcinoma. Findings here all support an improvement in overall survival for patients receiving steroid therapy during ICI treatment. This supports the association of immune related adverse events with improved survival among these cancer patients.

Figure 25: Overall survival for all diagnoses with toxicity event via ICD Codes, VA Data




Above in Figure 25, the effectiveness of ICD codes to identify toxicity events is assessed via a survival analysis among all cancer diagnoses, who had a recorded ICD code for a toxicity event during ICI therapy and up to 6 months post ICI therapy. As noted here, the survival is not different among these cohorts, suggesting potentially that ICD codes are not identifying toxicity events as well as prednisone therapy. Additional analyses to assess this finding are ongoing.

Below, in Figure 26, 1-year survival among all cancer diagnoses for patients with an ICD code defined toxicity event are presented. There is notable initial separation of survival curves early on in the survival analysis, suggesting potentially a short-lived effect on survival from an autoimmune toxicity.

Figure 26: All Diagnoses, 1 year survival by toxicity, VA Data

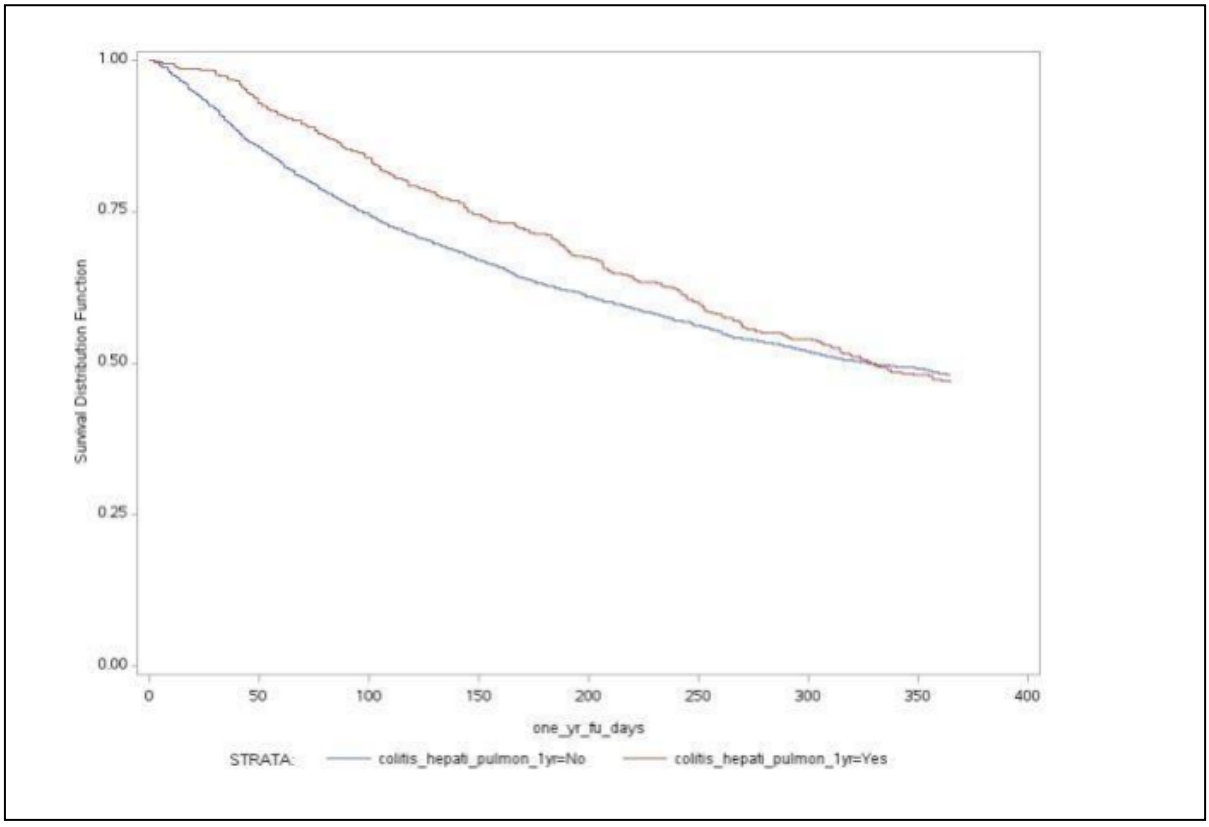
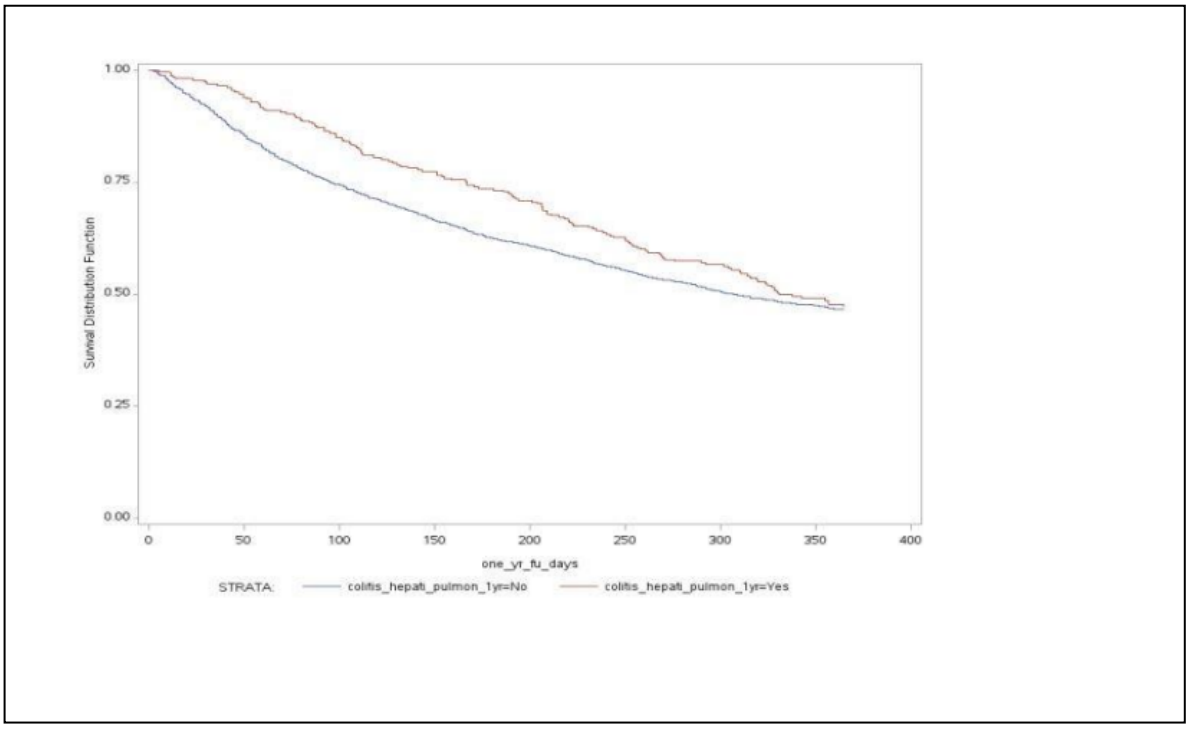



Figure 27: Overall survival among lung cancer patients among ICD code defined toxicity, VA Data



Above, in Figure 27, lung cancer patients were examined showing survival among patients with ICD code defined toxicity versus those without ICD code defined toxicity events.

- *Subtask 3: Calculate and compare PFS data for patients with and without grade 3/4 toxicities, utilizing Kaplan-Meier methods*
    - PFS has been a tough outcome to collect administratively and we have decided to limit the evaluation of PFS at this time. Abstraction allows PFS calculation, but has been time consuming and is not required for completion of alternate goals.
- *Subtask 4: Preparation and Publication of Manuscript*
    - This is ongoing. Publications to date are included in the Appendix.

## 4. Impact

***Current Impact*: We have found significant and potential novel findings along several avenues of investigation. Initial findings associating BMI with OS, and studies showing improved OS among those receiving steroids while on ICI therapy are important findings. Additionally the impact of the time of infusion of ICI has the potential to be a very significant finding that is currently leading to potential additional grant funding for prospective verification within the VA environment. Recent publication of findings from our lung cancer cohort looking at ICI related pneumonitis among patients receiving consolidation immunotherapy following definitive chemoradiation in NSLC are important findings. Furthermore, our evaluations over the past year of study funding have shown the validity of a frailty score at prediction of OS among ICI recipients. Ongoing abstraction continues over the course of a no-cost extension.**

***Potential Clinical Impact:*** The final product of the research will have significant impact on the understanding of clinical outcomes surrounding cancer immunotherapy, autoimmune related adverse events, and prognostic markers in the modern era of ICI therapy.

## 5. Changes/Problems

***Problems/Challenges Encountered*:** There have been several challenges encountered during the initial year of the grant. We will review these in depth here as well as the planned approach to overcome these complications.

> ***Uncertain Utility of ICD Codes to Identify Autoimmune Toxicities*:** The publication of a study from Ohio State bv *Nashed, Zhang, et al*, showing the inaccuracy of ICD codes for the detection of autoimmune related adverse events highlighted the potential complications of utilizing ICD codes to identify immune related adverse events. The inability to distinguish autoimmune events without extensive abstraction is a limiting factor to the current project and other similar retrospective/administrative data projects. *Planned Solution*: The current plan is for an approach utilizing steroid prescriptions to identify autoimmune toxicity events. Anecdotally, our clinical experience informs us that ICD codes for complications of therapy are infrequently entered by treating clinicians, and utilizing a prescription as a marker of an event should be a much more reliable approach. In this manner we hope to find a more sensitive and specific tool for identifying immune related adverse events. **To date, this approach has been successful and has been shown to be a reasonable and appropriate option in our fully abstracted VA Melanoma cohort. We are working to show this to be an appropriate approach in other cohorts at this time, abstraction is proceeding and further categories have been completed over the past year.**

***Chart Abstraction*:** Complicating the efforts above, chart abstraction has been a more complicated and time-consuming effort than initially expected. The initial plan to utilize resident physicians to complete chart reviews was complicated by training and regulatory requirements (predominately at the Veterans Affairs hospital), as well as increased clinical demands from the COVID-19 pandemic. *Planned Solution*: **We continue to add new team members for abstraction and are moving forward as quickly as we can in this regard. It remains challenging. However, we have made significant progress over the past year and will plan to utilize Prednisone prescriptions as well as we show these are associated with clear toxicities from treatment.**

***COVID-19 Related Challenges*:** As noted above, COVID-19 has clearly impacted the study in numerous ways. Increased workloads among the research team has limited time spent on chart abstraction as well as statistical analysis and oversight. The limitations on group meetings has changed the nature of collaboration. For the most part, we have been able to catch up from initial delays in the research and are now well-positioned to move forward.

***Limitations of Washington University in St. Louis Dataset*:** The dataset at Washington University in St. Louis is a very robust dataset, but runs currently only from 2016 through mid-2018. This leaves out 3 years of potential additional patients treated with ICI therapy. **We have received additional data from the WUSTL cohort, and this data is currently being cleaned and prepared for evaluation. Given the transition of the study to a no-cost extension, efforts at WUSTL are somewhat slower at this time.**

## 6. Products

***Final Product*:** The goal of this research and grant is to produce a risk prediction model for severe autoimmune toxicities from checkpoint inhibitor therapy among patients undergoing immunotherapy treatment for cancer. The utility of this tool will be significant, as it will allow clinicians to better counsel, select therapy and provide appropriate prognostic information for cancer patients. Additional goals of the research are to better explore predictors of toxicity, and predictors of overall survival among cancer patients. **We have produced substantial data and evidence to date regarding predictors of OS among ICI recipient cancer patients and continue to make progress at additional publications. The findings of time-of-infusion's association with OS are being translated into a potential prospective study funded through the VA (applications in development).**

***Progress Towards Final Product*:** As is outlined above under the Accomplishments section, significant progress has been made towards the goals of the grant. We have identified potential predictors of autoimmune toxicities and overall survival among cancer patients receiving immunotherapy. We have also made significant progress in the processing of our active datasets, as well as the training of our personnel to assist with ongoing research efforts. **We have found time of infusion to be a powerful predictor of OS among cancer patients receiving immune checkpoint inhibitors and are actively pursuing this unexpected discovery. This has the potential to open up new avenues of research in the coming months and beyond.**

***Publications*: Publications and abstracts are included in the addendum at this time. One publication was finalized this year, with additional publications in progress:**

**Akkad N, Thomas TS, Luo S, Knoche E, Sanfilippo KM, Keller JW. A real-world study of pneumonitis in non-small cell lung cancer patients receiving durvalumab following concurrent chemoradiation. Journal of Thoracic Disease. 2023.**

## 7. Participants & Other Collaborating Organizations

***St .Louis Veterans Affairs Medical Center:*** The St. Louis VA Medical Center remains an ongoing and active research site for this grant. A brief review of resources is outlined below:

Clinical Facilities: The John Cochran VA Medical Center is a full-service, level I health care facility. It provides both inpatient and ambulatory care with over 65 subspecialties including hematology/oncology. We are the largest hematology/oncology section in Missouri for Veterans to receive care. The majority of the patients served come from east central Missouri and southwestern Illinois.

Research Division: The staff for the research division involved in this proposal includes a full time statistician. Mrs. Luo has a Master degree in Public Health. She has over 15 years of experience as a statistician. She has expertise in analyses using SAS and is capable of using R and STATA as well. Given the space is shared with additional VA research teams, this offers an environment for collaboration and trouble shooting with other statisticians when needed in close proximity.

***Washington University in St. Louis*:** Washington University in St. Louis continues as an active participating site in the ongoing research. A brief updated overview of resources is outlined below:

***Clinical Facilities:***
*Barnes Jewish Hospital:* Barnes Jewish Hospital is the largest hospital in Missouri. The medical staff consists of over 1,800 attending physicians. The hospital contains 1,315 licensed beds providing care to over 50,000 admissions annually.

***Siteman Cancer Center:*** Siteman cancer center is the only National Cancer Institute designated Comprehensive Cancer Center in Missouri and within a 240-mile radius of St. Louis. Over 300 clinicians and researchers staff it. It is a member of the National Comprehensive Cancer Network. Given the distance to neighboring comprehensive centers, Siteman has a large referral basis with patients coming from all over the state to receive care.

***Research Facilities:*** Washington University in St. Louis is a world-class, robust research environment with extensive academic and research resources and ideal opportunities for collaboration.

**APPENDIX: Publications (Encl.)**

Original Article

# A real-world study of pneumonitis in non-small cell lung cancer patients receiving durvalumab following concurrent chemoradiation

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*Contributions:* (I) Conception and design: N Akkad, TS Thomas, JW Keller, E Knoche, KM Sanfilippo; (II) Administrative support: JW Keller; (III) Provision of study materials or patients: TS Thomas, JW Keller; (IV) Collection and assembly of data: N Akkad, TS Thomas; (V) Data analysis and interpretation: N Akkad, TS Thomas, S Luo; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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**Background:** Locally advanced non-small cell lung cancer (LA-NSCLC) treated with the programmed death-ligand 1 inhibitor durvalumab has been associated with significant rates of pneumonitis, which has led to higher rates of discontinuation of therapy in real-world populations. Thus far there has been no consensus in the literature on the impact of pneumonitis on survival.

**Methods:** This is a retrospective cohort study of veterans receiving durvalumab between 12/5/2017 and 4/15/2020. Participants were identified using VINCI data services. Patients were followed through 9/14/2021. Development of clinical pneumonitis was assessed through review of documentation and graded using CTCAE 4.0 criteria. Univariate logistic regression analysis evaluated for associations between body mass index (BMI), age, race, co-morbidity index, chemotherapy regimen, chronic obstructive pulmonary disease (COPD) severity, and development of clinical pneumonitis. Progression-free survival (PFS) and overall survival (OS) were evaluated using Kaplan-Meier methods. Cox proportional hazards models were utilized to evaluate the association between risk of death at 1 and 2 years and candidate predictor variables.

**Results:** A total of 284 patients were included in this study. Sixty-one patients developed clinically significant pneumonitis, 7 patients developed grade 5 pneumonitis (death from pneumonitis). The median OS in patients that developed pneumonitis was 27.8 *vs.* 36.9 months in patients that did not develop pneumonitis (P=0.22). BMI was found to be a clinical predictor of pneumonitis (P=0.04). COPD severity, race, age at durvalumab start date, chemotherapy regimen, and Romano comorbidity index were not significant predictors of pneumonitis. Cox proportional hazards analysis failed to demonstrate an association between the development of pneumonitis and risk of death in this population.

**Conclusions:** The incidence of clinically significant pneumonitis is higher than noted in the PACIFIC trial in this cohort, however this high rate of pneumonitis does not have an impact on OS or PFS. Obesity was found to be a significant predictor of pneumonitis in this patient population.

**Keywords:** Checkpoint inhibitors; immunotherapy; toxicities; non-small cell lung cancer (NSCLC); chemoradiotherapy

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## Introduction

Locally advanced non-small cell lung cancer (LA-NSCLC) comprises approximately one-third of new NSCLC diagnoses. After the results of the PACIFIC trial, unresectable disease is treated with definitive intent concurrent chemoradiation (CRT) followed by the programmed death-ligand 1 (PD-L1) inhibitor durvalumab given higher overall survival (OS) and progression-free survival (PFS) with the addition of durvalumab (1-3). As such, durvalumab following completion of CRT has become standard of care.

Immune checkpoint inhibitors are associated with a variety of complications. In patients receiving durvalumab for NSCLC, pneumonitis has been shown to be one of the most common (4). This inflammatory condition of the lungs is a potentially fatal adverse effect of immunotherapy or radiation therapy, therefore the risk of pneumonitis is a key concern. The incidence of clinically important, grade 3/4 pneumonitis in the landmark PACIFIC trial was 3.4% (compared to 2.6% with placebo), and the rate of any grade pneumonitis was 19% (1). In clinical practice, the observed rate of clinically significant pneumonitis is higher (5). Smaller real-world cohorts have reported the rate of any grade pneumonitis as anywhere from 19–35% (6-8). The reported incidence of clinically significant grade 3 or higher pneumonitis has been reported from 6% to 15% in smaller real-world cohorts and larger meta-analyses (7,9,10). Death from pneumonitis (grade 5 toxicity) while rare (reported incidence around 1%) represents a serious consequence of therapy (11). Altogether these studies suggest that pneumonitis is more common in real-world settings than reported in clinical trials. Our study sought to explore the frequency of pneumonitis, the impact of pneumonitis on survival, and explore clinical predictors of pneumonitis in a real-world cohort of US veterans.

Previous studies have evaluated some clinical and laboratory predictors of pneumonitis. The following characteristics including chemotherapy choice (6), lung volume receiving >20 Gy (V20), sex, age, smoking status, presence of baseline pneumonitis, type of radiation, location of lesion (12), PD-L1 expression (13), dose of durvalumab, Eastern Cooperative Oncology Group (ECOG) performance status, histology, time between radiation and durvalumab, relevant co-morbidities (14), and Brinkman index (15) have not been found to be predictive of pneumonitis. There has been some incongruity in the literature however as some studies have found that V20, V40, V5, mean lung dose, and history of pneumonitis prior to durvalumab administration (16) are risk factors for grade 2 or greater pneumonitis, while others have found the opposite (11,17-19). Taken together, reliable clinical and laboratory markers predictive of pneumonitis development have not been consistently reported. No large multi-institutional studies have evaluated chronic obstructive pulmonary disease (COPD) severity, though in a single institution presence of baseline COPD was found to be a risk factor for developing pneumonitis (20). Body mass index (BMI) has never been evaluated as a potential clinical predictor of pneumonitis development.

The clinical impact of pneumonitis on patients receiving durvalumab is that they have higher rates of discontinuation of therapy (5,21). Both discontinuation of therapy and development of pneumonitis may impact survival. One real world study showed that patients that experienced any grade pneumonitis had a lower 12-month OS, while others have shown that grade 2 or higher pneumonitis does not appear to be associated with worse OS or PFS (10,21). Given the high incidence of pneumonitis in this patient population and unclear impact on survival, this study evaluates the incidence of pneumonitis and survival in a large nationwide real-world cohort of United States Veterans. This will become increasingly important in order to help make decisions about continuing *vs.* stopping durvalumab therapy in patients with pneumonitis. We present this article in

### Highlight box

**Key findings**

- Pneumonitis secondary to durvalumab administration in patients with non-small cell lung cancer does not impact overall survival or progression-free survival.
- Obesity is a significant predictor of pneumonitis in this patient population.

**What is known and what is new?**

- Incidence of pneumonitis is higher in real world patients receiving durvalumab than the PACIFIC trial and causes discontinuation of therapy.
- Pneumonitis secondary to durvalumab does not lead to higher rates of death.
- Patients with a higher body mass index (BMI) are more likely to develop pneumonitis secondary to durvalumab therapy.

**What is the implication, and what should change now?**

- Incident pneumonitis was not associated with increased risk of death in this population, even among patients with severe chronic obstructive pulmonary disease. Higher risks of pneumonitis should be discussed with patients with a high BMI.

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accordance with the STROBE reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-22-1604/rc).

## Methods

Veterans receiving durvalumab between 12/5/2017 and 4/15/2020 were identified using VA Informatics and Computing Infrastructure (VINCI) data services. Only patients with NSCLC who received CRT and at least once dose of durvalumab were included. Individual patient records were reviewed using the Compensation and Pension Records Interchange software system/Joint Legacy Viewer. Patients were followed through 9/14/2021. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Veterans Affairs St. Louis Healthcare System Institutional Review Boards (IRB No. 1625948-6) and individual consent for this retrospective analysis was waived.

This is a multi-center, population-based, retrospective cohort study evaluating patients with NSCLC treated with durvalumab following completion of concurrent CRT. Oncologic treatment history including chemotherapy received, dates and doses of durvalumab administration, radiation treatment history, date of progression, pulmonary function tests, PD-L1 percentage, BMI, and date of death were recorded through manual chart review (N.A. and T.S.T.).

The primary outcome of interest was development of clinical pneumonitis. This was assessed through review of documentation from oncology and pulmonology providers. Imaging reports were reviewed to assess for the presence of infiltrates. Pneumonitis grade was obtained directly from the medical record when available. If missing, clinical documents in combination of prescription of corticosteroids and supplemental oxygen administration were interpreted and graded using Common Terminology Criteria for Adverse Events (CTCAE) 4.0 criteria. Patients with new radiographic infiltrates without documented clinical pneumonitis are considered asymptomatic, potential pneumonitis patients. Receipt of corticosteroids was confirmed through pharmacy records. COPD severity was graded based on the American Thoracic Society categories from 2005. The Romano adaptation of the Charlson comorbidity index was calculated using International Classification of Diseases, Ninth Revision (ICD-9) codes to develop a composite comorbidity score (22).

### *Statistical analyses*

Univariate logistic regression analysis evaluated for associations between age, race, Romano co-morbidity score, chemotherapy regimen, COPD severity [determined by recorded forced expiratory volume in 1 second (FEV1)], BMI, and development of clinical pneumonitis. Cox proportional hazards analysis was used to estimate hazard ratios for risk of death up to 1 and 2 years from durvalumab start date and controlling for potentially confounding variables (age, clinical stage, co-morbidities, and pneumonitis). Cox proportional hazards analysis was performed to estimate hazard ratios to evaluate risk of death at 2 years including age, co-morbidities, race, chemotherapy, time from radiation to durvalumab initiation, COPD severity, and obesity (<30 *vs.* ≥30 kg/m$^2$ BMI). PFS and OS (stratified by clinical pneumonitis) were evaluated using Kaplan-Meier methods. Survival curves were made using date of first durvalumab through 9/14/2021 as the specified time period. Statistical analyses were performed using SAS version 9.2 (SAS Institute, Cary, NC, USA).

## Results

There were 284 patients with NSCLC at the Veterans Health Administration (VHA) who received CRT followed by durvalumab between 12/5/2017 and 4/15/2020. Of these patients, 1 was stage I, 21 were stage II, 228 were stage III, the rest were unknown (*Table 1*). The majority of patients had either adenocarcinoma (125 patients) or squamous cell carcinoma (132 patients). The median age at diagnosis was 68 for all patients included. Of the patients that PD-L1 expression was checked and recorded (112 patients), 39 had <1% PD-L1 expression, 41 had between 11% and 49% expression, and 32 had greater than 50% expression. Regarding co-morbidities, of this patient population 33% had type 2 diabetes, 10% had renal failure, and 18% had a prior autoimmune disease. Baseline FEV1 data was also collected on these patients. Fifty-one patients had a normal FEV1, 33 had a mild impairment, 31 had a moderate impairment, 37 had a moderately severe impairment, 31 had a severe impairment and 17 had a very severe impairment, 84 were unknown. Chemotherapy regimen and radiation dose are summarized in *Table 1*. Carboplatin and paclitaxel was administered most commonly to 80% of patients. In total, 59% of patients received >54 Gy of radiation. Durvalumab was completed in 101 (35%) of patients

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**Table 1** Patient demographics

| Characteristics | Value (n=284) |
|---|---|
| Age (years), median [range] | 68 [39–88] |
| Male, n [%] | 271 [96] |
| Charlson score, mean | 4.6 |
| BMI (kg/m$^2$), median | 26.0 |
| BMI (kg/m$^2$), n [%] | |
| ≥30 | 67 [24] |
| <30 | 217 [76] |
| Stage, n [%] | |
| I | 1 [<1] |
| II | 21 [7] |
| III | 228 [80] |
| Unknown | 35 [12] |
| Histology, n [%] | |
| Adenocarcinoma | 125 [44] |
| Squamous cell | 132 [46] |
| Poorly differentiated | 21 [7] |
| Mixed | 1 [<1] |
| Large cell | 2 [1] |
| NOS | 2 [1] |
| PD-L1 expression, n [%] | |
| <1% | 39 [14] |
| 11–49% | 41 [14] |
| >50% | 32 [11] |
| Unknown | 172 [61] |
| PFTs, n [%] | |
| No impairment | 51 [18] |
| Mild (FEV1 70–79%) | 33 [11] |
| Moderate (FEV1 60–69%) | 31 [11] |
| Moderately severe (FEV1 50–59%) | 37 [13] |
| Severe (FEV1 35–49%) | 31 [11] |
| Very severe (FEV1 <35%) | 17 [6] |
| Unknown | 84 [30] |
| Chemotherapy regimen, n [%] | |
| Carboplatin/paclitaxel | 226 [80] |
| Platinum/pemetrexed | 25 [9] |
| Platinum/etoposide | 20 [7] |
| Platinum/vinorelbine | 1 [<1] |
| Unknown or none | 12 [4] |
| Radiation dose, n [%] | |
| <54 Gy | 9 [3] |
| 54–66 Gy | 140 [49] |
| >66 Gy | 28 [10] |
| Unknown | 107 [38] |
| Reason for durvalumab discontinuation, n [%] | |
| Therapy completed | 101 [35] |
| Progression | 84 [30] |
| Toxicity | 59 [21] |
| Patient decision | 23 [8] |
| Death | 128 [45] |
| Therapy ongoing | 2 [1] |
| Unknown | 4 [1] |

BMI, body mass index; NOS, not otherwise specified; PD-L1, programmed death-ligand 1; PFTs, pulmonary function tests; FEV1, forced expiratory volume in 1 second.

**Table 2** Toxicities

| Toxicity | Value (n=284) |
|---|---|
| Pneumonitis, n [%] | |
| Grade 2 | 25 [9] |
| Grade 3 | 26 [9] |
| Grade 4 | 3 [1] |
| Grade 5 | 7 [2] |
| Hepatitis, n [%] | 2 [1] |
| Endocrinopathy, n [%] | 13 [5] |
| Colitis, n [%] | 2 [1] |
| Hypersensitivity reaction, n [%] | 5 [2] |
| Arthralgia, n [%] | 1 [<1] |

and was ongoing at time of review in 2 patients (1%). Durvalumab was discontinued due to disease progression in 84 patients (30%) and toxicity in 59 patients (21%).

All reported toxicities are summarized in *Table 2*. Sixty-one patients developed clinically significant pneumonitis, defined as grade 2 or higher. One hundred and six patients developed imaging changes possibly consistent with pneumonitis, but of these only 9 were clinically defined as grade 1 pneumonitis in electronic medical record

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**Table 3** Grade 5 pneumonitis

| No. | Stage | Histology | Time to pneumonitis (days) | Treatment | Other irAE |
|---|---|---|---|---|---|
| 1 | T3N2M0 | SCC | 28 | Steroids + infliximab | Arthritis |
| 2 | T4NxMx | SCC | 209 | Steroids | No |
| 3 | T2N2M0 | Adeno | 26 | Unknown | No |
| 4 | T0N3M0 | Adeno | 6 | Steroids | No |
| 5 | Unknown | SCC | 20 | Steroids | No |
| 6 | T4N2M0 | Mixed (SCC + adeno) | 20 | Steroids | No |
| 7 | T3N2M0 | SCC | 28 | Infliximab | No |

irAE, immune related adverse event; SCC, squamous cell carcinoma; adeno, adenocarcinoma.

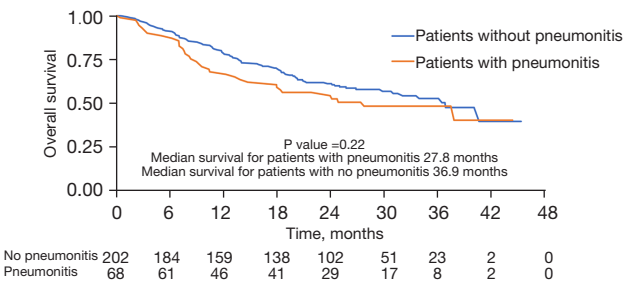


**Figure 1** Kaplan-Meier curve showing OS in patients receiving durvalumab for NSCLC that developed pneumonitis *vs.* those that did not up to 48 months. OS, overall survival; NSCLC, non-small cell lung cancer.

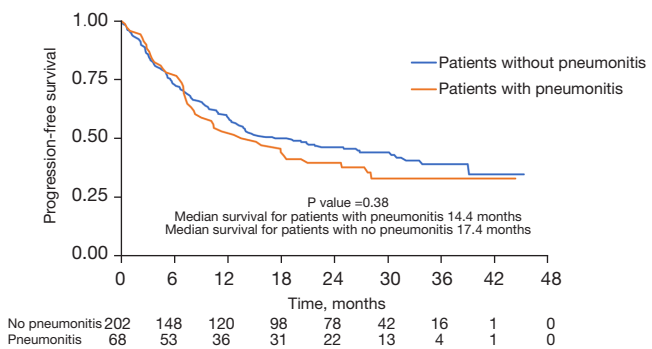


**Figure 2** Kaplan-Meier curve showing PFS in patients receiving durvalumab for NSCLC that developed pneumonitis *vs.* those that did not up to 48 months. PFS, progression-free survival; NSCLC, non-small cell lung cancer.

(EMR) notes. Of the total cohort 9% developed grade 2 pneumonitis, 9% developed grade 3 pneumonitis, 1% developed grade 4 pneumonitis, and 2% developed grade 5 pneumonitis. Most patients who developed pneumonitis did not resume durvalumab. Nineteen patients (27%) who developed clinically significant pneumonitis were re-challenged. Of these re-challenged patients, 15 patients (79%) tolerated durvalumab without re-developing pneumonitis. Two patients got pneumonitis a second time and therapy was stopped again. Other toxicities noted in this study were endocrinopathies (13 patients), hepatitis (2 patients), colitis (2 patients), hypersensitivity reactions (5 patients), and arthritis (1 patient). Characteristics of patients that developed grade 5 pneumonitis are shown in *Table 3*. Of note, median time to pneumonitis in these patients was 26 days and the majority were treated with steroids.

The median OS in patients that developed pneumonitis (including 9 defined as grade 1), compared to those who did not was 27.8 and 36.9 months (P=0.22), respectively (*Figure 1*). Similarly PFS was not significantly different in patients who developed pneumonitis *vs.* those that did not (14.4 *vs.* 17.4 months, P=0.38) (*Figure 2*). Our study additionally looked at clinical and laboratory predictors of pneumonitis and found that patients with a BMI ≥30 kg/m$^2$ were more likely to develop pneumonitis than patients with a BMI <30 kg/m$^2$ [odds ratio (OR): 1.87; 95% confidence interval (CI): 1.01 to 3.47; P=0.04]. Other clinical predictors including COPD severity, race, age at durvalumab start date, chemotherapy regimen, and Romano comorbidity score were not significant predictors of pneumonitis (*Table 4*). Cox proportional hazards analysis failed to demonstrate an association between the development of pneumonitis and risk of death. Our study also evaluated age, co-morbidities, race, chemotherapy, time from radiation to durvalumab initiation, COPD Severity, and obesity (<30 *vs.* ≥30 kg/m$^2$ BMI) as risk factors for death at 2 years and found that they were not clinically significant predictors.

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**Table 4** Clinical predictors of pneumonitis

| Characteristics | Risk factors | OR | 95% CI |
|---|---|---|---|
| BMI (kg/m$^2$) | ≥30 (*vs.* <30) | 1.87 | 1.01–3.47 |
| Age (years) | 60–69 (*vs.* <60) | 1.15 | 0.43–3.10 |
| | >70 (*vs.* <60) | 1.67 | 0.63–4.46 |
| Co-morbidities | Romano co-morbidity index | 1.03 | 0.93–1.15 |
| Race | Black (*vs.* White) | 0.81 | 0.38–1.74 |
| | Other (*vs.* White) | 0.97 | 0.10–9.52 |
| Chemotherapy | Platinum + pemetrexed (*vs.* carbo/taxol) | 2.43 | 1.02–5.82 |
| | Platinum + etoposide (*vs.* carbo/taxol) | 1.46 | 0.53–4.00 |
| Time from radiation to durvalumab initiation (days) | 30 (*vs.* 31–45) | 1.26 | 0.56–2.87 |
| | 46–60 (*vs.* 31–45) | 1.94 | 0.85–4.39 |
| | 61 (*vs.* 31–45) | 1.46 | 0.67–3.18 |
| COPD severity | Mild impairment (*vs.* none) | 2.29 | 0.87–6.00 |
| | Moderate impairment (*vs.* none) | 0.66 | 0.21–2.11 |
| | Moderate to severe impairment (*vs.* none) | 1.79 | 0.70–4.58 |
| | Severe impairment (*vs.* none) | 0.86 | 0.28–2.63 |
| | Very severe impairment (*vs.* none) | 0.97 | 0.27–3.56 |

OR, odds ratio; CI, confidence interval; BMI, body mass index; COPD, chronic obstructive pulmonary disease.

## Discussion

In this multi-center, population-based retrospective cohort study of US veterans with NSCLC treated with durvalumab, the incidence of clinically significant pneumonitis (defined as grade 2 or higher) was 21% which included 13% with grade 3 or higher pneumonitis. In the landmark PACIFIC trial, grade 3/4 pneumonitis occurred in 3.4% of patients[2]. Prior studies have similarly demonstrated a higher incidence of pneumonitis then reported in clinical trials (7,9,10). Interestingly, in our cohort, 7 patients had grade 5 pneumonitis and died from these complications. The PACIFIC trial did not report grade 5 pneumonitis (1). Our study also shows a higher rate of grade 5 pneumonitis than what has been reported in other real-world studies, with others reporting the rate of grade 5 pneumonitis around 1% (11). This highlights the fact that in real-world populations, pneumonitis is more prevalent and more severe. This may be due to the fact that real-world populations include a more frail patient population with more co-morbidities than clinical trial populations. However, our study shows that pneumonitis does not affect OS or PFS across all patients. The current literature has not been consistent if pneumonitis has an effect on survival, our study is one the largest populations in which survival has been evaluated, with no clear association found between OS and pneumonitis incidence among this population.

Our study also found that obesity is a predictor of pneumonitis development in patients receiving durvalumab. Patients with a BMI ≥30 kg/m$^2$ had a significantly increased risk of developing pneumonitis. Obesity has not been previously evaluated as a clinical predictor of pneumonitis in this patient population. This suggests that providers should monitor for development of pneumonitis when administering durvalumab in patients with elevated BMIs. The mechanism of this is not yet known, however, a study by Katsui *et al.* suggests dysfunctional adipocytes in obese patients have increased adipocytokine production including interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α), leading to a state of chronic inflammation (23). This baseline elevated cytokine production may lower the threshold needed to cause the inflammatory response for durvalumab mediated pneumonitis. Other clinical predictors evaluated in this study including COPD severity, race, age at durvalumab start date, chemotherapy regimen, and Romano comorbidity score were not found to be significant predictors of pneumonitis development. COPD severity has not been previously evaluated as a predictor of pneumonitis in this

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population, however it does not appear to be a risk factor, meaning a severe impairment should not prohibit clinicians from administering durvalumab to these patients. This is in contrast to Thomas *et al.* (20) who showed that baseline COPD was a risk factor in the development of radiation of immune related pneumonitis in their cohort of 39 patients. Our study shows in a larger patient population and taking into account the severity of COPD, this risk factor does not have an impact of the development of pneumonitis.

Together this study confirms higher rates of clinically significant pneumonitis in a multi-center real world population that other studies have shown. This study also suggests that the risk of potentially fatal pneumonitis is not minimal, and clinicians should carefully discuss this risk with individual patients while closely monitoring for this potentially deadly adverse event. Our study found there is no association between pneumonitis and risk of death up to 1 or 2 years when age, cancer stage and co-morbidities are taken into account. However, durvalumab was discontinued in most patients who developed pneumonitis. Whether there will be long term impacts on survival due to this discontinuation requires longer follow up. There was no difference in PFS suggesting that disease control was not impacted by the discontinuation of durvalumab.

Additionally, our study reports 5 patients who had a hypersensitivity reaction (2%) while receiving durvalumab. The incidence of hypersensitivity reactions has not been previously reported in the literature in NSCLC patients receiving durvalumab to our knowledge. This is clinically significant as two reactions resulted in hospitalizations. Hypersensitivity reactions to durvalumab are potentially under recognized. This is an important aspect of treatment that clinicians should be aware of as it is treatable with prompt interventions during infusion.

This study included patients that were majority male given the patient population was patients receiving care at the VA, meaning this data may not be generalizable to a female patient population. Additionally, grade 1 immune related pneumonitis and radiation pneumonitis do not have clear guidelines to differentiate the two, meaning our study may have underestimated the prevalence of grade 1 pneumonitis due to durvalumab therapy in this patient population. Additionally, our study may have included pneumonitis secondary to radiation *vs.* durvalumab for the same reason.

## Conclusions

In conclusion, this study confirms that rates of clinically significant pneumonitis are higher than noted in the PACIFIC trial in NSCLC patients receiving durvalumab. However as has been inconsistent in the literature, this high rate of pneumonitis does not have an impact on OS or PFS. This study also found obesity (defined as a BMI $\geq$30 kg/m$^2$) to be a clinical predictor of pneumonitis.

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## Footnote

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*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Veterans Affairs St. Louis Healthcare System Institutional Review Boards (IRB No. 1625948-6) and individual consent for this

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retrospective analysis was waived.

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